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(54) Pyrazolopyridine compound and processes for preparation thereof

Pyrazolopyridinverbindung und Verfahren zu ihrer Herstellung

Composé de pyrazolopyridine et procédés pour sa préparation

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(56) References cited:
EP-A- 0 299 209
EP-A- 0 379 979
GB-A- 2 057 438

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Description

The present invention relates to novel pyrazolopyridine compound and a pharmaceutically acceptable salt thereof.

More particularly, it relates to novel pyrazolopyridine compound and a pharmaceutically acceptable salt thereof, which are adenosine antagonists and possess various pharmaceutical actions such as cognitive enhancing action, analgesic action, locomotor action, antidepressant action, cerebral vasodilating action, diuretic action, cardiotonic action, vasodilating action, the action of increasing the renal blood flow, renal prophylactic effect, improvemental effect of renal function, enhanced lipolysis action, inhibited anaphylactic bronchoconstrictive action, accelerating action of the release of insulin, antiulcerative action, or protective effect against pancreatitis, and so are useful as psychostimulant, analgesic, antidepressant, ameliorants of cerebral circulation, drug for heart failure, cardiotonic agent, antihypertensive agent, drug for renal insufficiency (renal failure), drug for renal toxicity, renal prophylactic agent, improvemental agent of renal function, diuretic, drug for edema, antiobesity, antiasthmatic, bronchodilater, drug for apnea, drug for gout, drug for hyperuricemia, drug for sudden infant death syndrome (SIDS), ameliorants of immunosuppresion action of adenosine, antidiabetic agent, antiulcerative agent, or drug for pancreatitis, and further which are inhibitors of platelet aggregation, so are useful as drug for thrombosis, drug for myocardiac infarction, drug for obstruction, drug for arteriosclerosis obliterans, drug for thrombophlebitis, drug for cerebral infarction, drug for transient ischemic attack, or drug for angina pectoris; to a process for preparation thereof, to a pharmaceutical composition comprising the same, and to a method for using the same therapeutically in human being and animals for the prevention and/or treatment of melancholia, heart failure, hypertension (e.g. essential hypertension, nephrogenous hypertension), renal insufficiency (renal failure) (e.g. acute renal failure), renal toxicity [e.g. renal toxicity (damage of kidney) induced by a drug such as cisplatin, gentamicin, FR-900506 (disclosed in EP-0184162), or cyclosporins (e.g. cyclosporin A); glycerol], nephrosis, nephritis, edema (e.g. cardiac edema, nephrotic edema, hepatic edema, idiopathic edema, drug edema, acute angioneurotic edema, hereditary angioneurotic edema, and carcinomatous ascites, gestational edema), obesity, bronchial asthma, gout, hyperuricemia, sudden infant death syndrome, immunosuppresion, diabetes, ulcer such as peptic ulcer (e.g. gastric ulcer, and duodenal ulcer), pancreatitis, myocardiac infarction, thrombosis (e.g. arterial thrombosis, and cerebral thrombosis), obstruction, arteriosclerosis obliterans, thrombophlebitis, cerebral infarction, transient ischemic attack, and angina pectoris.

EP-A-0 299 209 and EP-A-0 379 979 both disclose pyrazolopyridine compounds and pharmaceutical preparations thereof.

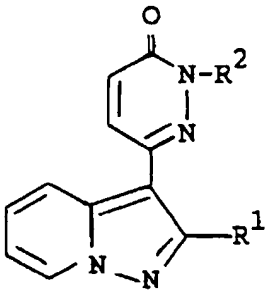
Accordingly, one object of the present invention is to provide the novel pyrazolopyridine compound and a pharmaceutically acceptable salt thereof, which are useful as stated above.

Another object of the present invention is to provide processes for the preparation of the novel pyrazolopyridine compound or a salt thereof.

A further object of the present invention is to provide a pharmaceutical composition comprising, as an active ingredient, said pyrazolopyridine compound or a pharmaceutically acceptable salt thereof.

Still further object of the present invention is to provide a method for using said pyrazolopyridine compound as aforesaid therapeutic use, which comprises administering said pyrazolopyridine compound to human being or animals.

The novel pyrazolopyridine compound of the present invention can be shown by the following formula (I).

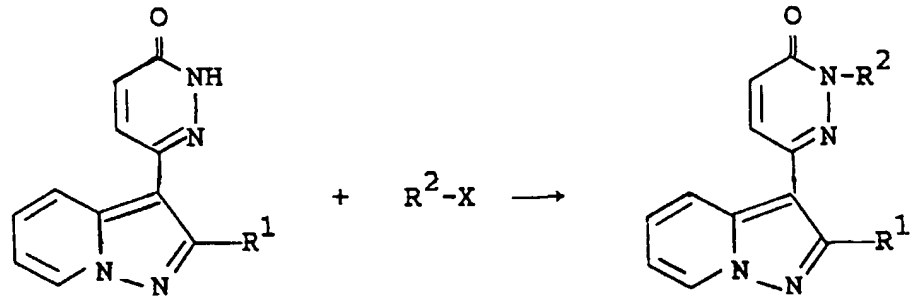


(I)

wherein R^1 and R^2 are as defined in claim 1.

The object compound (I) or a salt thereof can be prepared according to the following reaction schemes.

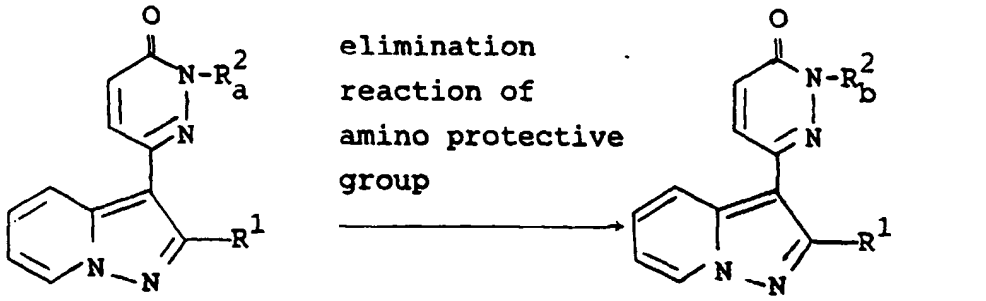
Process 1



(II) (III) (I)

or a salt thereof or a salt thereof or a salt thereof

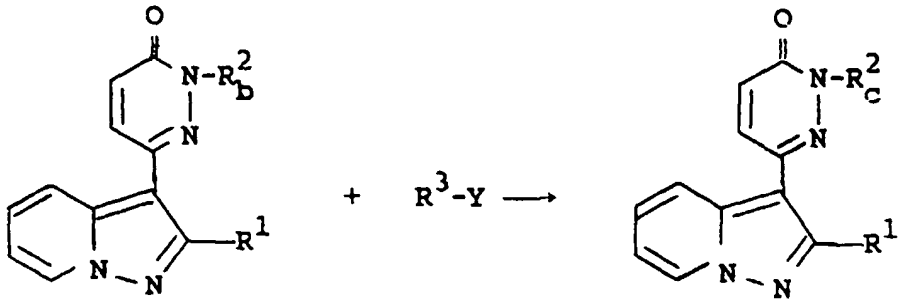
Process 2



(Ia)
or a salt thereof

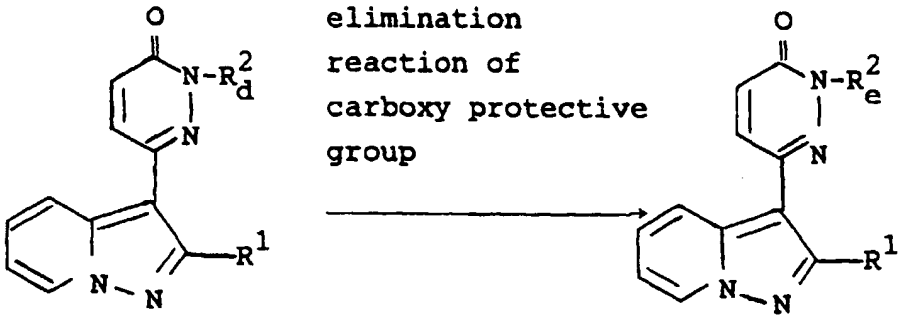
(Ib)
or a salt thereof

Process 3



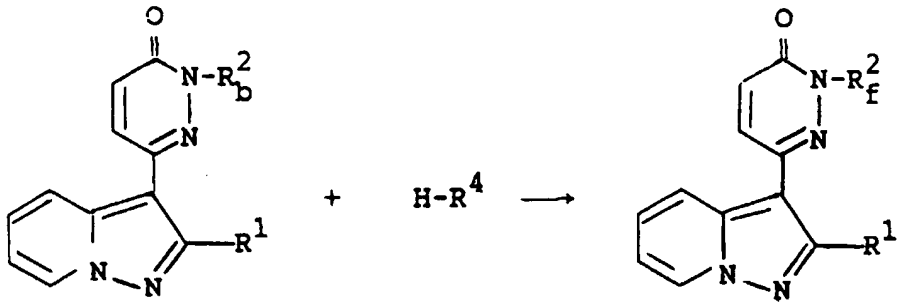
(Ib) or a salt thereof + (IV) or a salt thereof → (Ic) or a salt thereof

Process 4



(Id) or a salt thereof → (Ie) or a salt thereof

Process 5

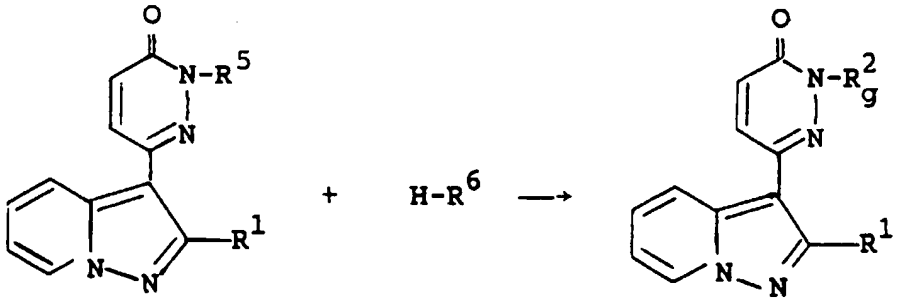


(Ib)
or a salt thereof

(V)

(If)
or a salt thereof

Process 6

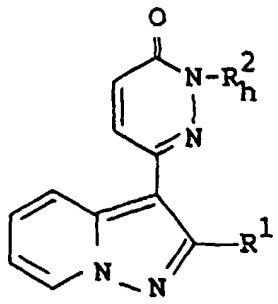


(VI)
or its reactive derivative at hydroxy group
or a salt thereof

(VII)
or a salt thereof

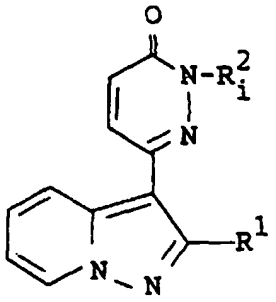
(Ig)
or a salt thereof

Process 7



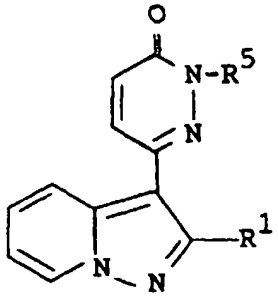
(Ih)
or a salt thereof

formation reaction of tetrazolyl group



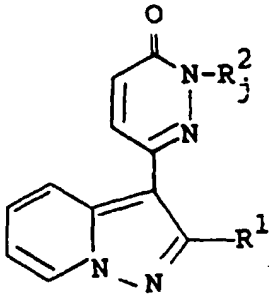
(Ii)
or a salt thereof

Process 8



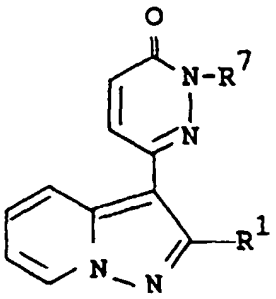
(VI)
or a salt thereof

dehydration reaction



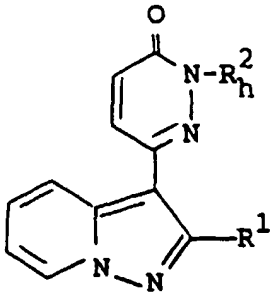
(Ij)
or a salt thereof

Process 9



(VIII)
or a salt thereof

cyanation reaction



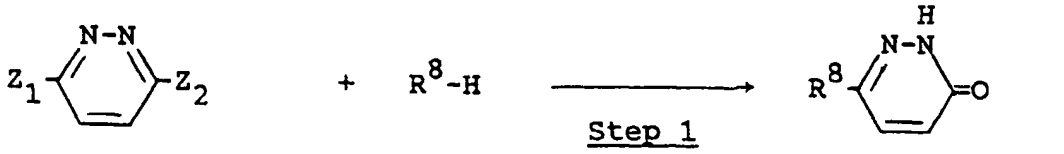
(Ih)
or a salt thereof

wherein R^1, R^2 are each as defined in claim 1. R^2_a, R^2_b, R^2_c, R^2_d, R^2_e, R^2_f, R^2_g, R^2_h, R^2_i, R^2_j, R^3, R^4, R^5, R^6, R^7, x and y are each as defined in claim 3 of the set of claims for all designated states except ES and GR and as in claim 1 of the set of claims for ES and GR respectively.

Among the starting compounds, the compounds (II), (VI) and (VIII) are novel.

The compound (II) can be prepared, for example, by the following reaction schemes.

Process A



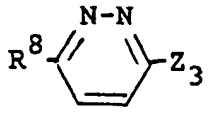
(IX) or a salt thereof

(X) or a salt thereof

(XI) or a salt thereof

halogenation reaction

Step 2

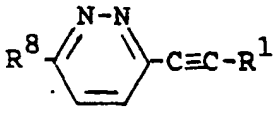


+ R^1-C≡CH

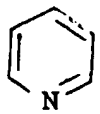
(XII) or a salt thereof

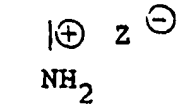
(XIII) or its reactive derivative or a salt thereof

Step 3



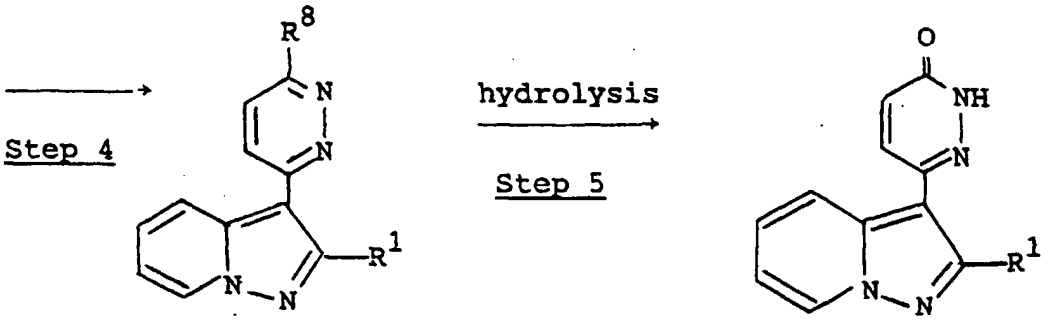
+





(XIV) or a salt thereof

(XV)



(XVI)
or a salt thereof

(II)
or a salt thereof

wherein

R^1 is as defined above,

R^8 is arylsulfonyl which may have one or more suitable substituent(s), di(C_1-C_6)alkylamino, C_1-C_6-alkoxy, C_1-C_6-alkylthio or acyloxy,

Z_1, Z_2 and Z_3 are each halogen, and

$Z^{\ominus}$ is an anion.

The compounds (VI) and (VIII) can be prepared according to the methods disclosed in Preparations described later or the similar manners thereto.

Suitable pharmaceutically acceptable salts of the object compound (I) are conventional ones and include a metal salt such as an alkali metal salt (e.g. sodium salt, and potassium salt) and an alkaline earth metal salt (e.g. calcium salt, and magnesium salt), an ammonium salt, an organic base salt (e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, and N,N'-dibenzylethylenediamine salt), an organic acid salt (e.g. acetate, trifluoroacetate, maleate, tartrate, fumalate, methanesulfonate, benzenesulfonate, formate, and toluenesulfonate), an inorganic acid salt (e.g. hydrochloride, hydrobromide, hydroiodide, sulfate, and phosphate), a salt with an amino acid (e.g. arginine, aspartic acid, and glutamic acid).

In the above and following descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention includes within the scope thereof are explained in detail as follows.

The term "lower" is means 1 to 6 carbon atom(s).

The term "higher" means 7 to 20 carbon atoms.

Suitable "aryl" include phenyl, tolyl, xylyl, and naphthyl, in which the preferred one may be phenyl.

Suitable "amino(lower)alkyl" may include aminomethyl, 1-aminoethyl, 2-aminoethyl, 2-aminopropyl, 3-aminobutyl, 2-amino-1,1-dimethylethyl, 5-aminopentyl, and 1-aminohexyl, in which the preferred one may be amino(C_1-C_4)alkyl and the more preferred one may be 2-aminoethyl.

Suitable "lower alkylamino(lower)alkyl" may include mono- or di- (lower)alkylamino(lower)alkyl" such as methylaminomethyl, 2-(ethylamino)ethyl, 3-(propylamino)propyl, 2-(propylamino)butyl, 2-(t-butylamino)-1,1-dimethylethyl, 4-pentylaminopentyl, 6-hexylaminohexyl, dimethylaminomethyl, 2-dimethylaminoethyl, 1-(N-methylethylamino)ethyl, 1-dimethylaminopropyl, 2-diethylaminopropyl, 3-dimethylaminopropyl, 3-(N-propylbutylamino)butyl, 4-dimethylaminobutyl, 2-dibutylamino-1,1-dimethylethyl, 4-dipentylaminopentyl, or 6-(N-pentylhexylamino)hexyl; in which the preferred one may be di(lower)alkylamino(lower)alkyl, the more preferred one may be di(C_1-C_4)alkylamino(C_1-C_4)alkyl and the most preferred one may be 2-dimethylaminoethyl, 3-dimethylaminopropyl and 4-dimethylaminobutyl.

Suitable "carboxy(lower)alkylamino(lower)alkyl" may include carboxymethylaminomethyl, 2-(carboxymethylamino)-ethyl, 2-(1-carboxyethylamino)ethyl, 3-(2-carboxypropylamino)propyl, 2-(3-carboxypropylamino)-butyl, 2-(2-carboxy-1,1-dimethylethylamino)-1,1-dimethylethyl, 4-(5-carboxypentylamino)pentyl, or 6-(3-carboxyhexylamino)hexyl, in which the preferred one may be carboxy(C_1-C_4)alkylamino(C_1-C_4)alkyl and the most preferred one may be 2-(carboxymethylamino)ethyl.

Suitable "C_1-C_6-alkoxycarbonyl(lower)alkylamino(lower)alkyl" may be the methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, tert-butyl ester, pentyl ester, hexyl ester, and 1-cyclopropylethyl ester].

Suitable lower alkoxycarbonyl(lower)alkylamino(lower)alkyl may be methoxycarbonylmethylaminomethyl, 2-

(ethoxycarbonylmethylamino)ethyl, 2-(1-ethoxycarbonylethylamino)ethyl, 3-(2-propoxycarbonylpropylamino)propyl, 2-(3-butoxycarbonylpropylamino)butyl, 2-(2-t-butoxycarbonyl-1,1-dimethylethylamino)-1,1-dimethylethyl, 4-(5-pentyloxycarbonylpentylamino)-pentyl, or 6-(3-hexyloxycarbonylhexylamino)hexyl; the more preferred one may be (C_1-C_4) alkoxycarbonyl(C_1-C_4)alkylamino(C_1-C_4)alkyl, and the most preferred one may be 2-(ethoxycarbonylmethylamino) ethyl.

Suitable "lower alkylamino(lower)alkyl having hydroxy and naphthyloxy" may be aforesaid "lower alkylamino(lower) alkyl" having "hydroxy" and "naphthyloxy" and suitable examples thereof may include 1-(1-naphthyloxy)-1-hydroxymethylaminomethyl, 2-[2-hydroxy-3-(1-naphthyloxy)propylamino]ethyl, 2-[4-hydroxy-1-(2-naphthyloxy)butylamino]-1,1-dimethylethyl, 4-[1-hydroxy-5-(1-naphthyloxy)pentylamino]-pentyl, 6-[2-hydroxy-4-(2-naphthyloxy)hexylamino]hexyl, in which the preferred one may be (C_1-C_4)alkylamino(C_1-C_4)-alkyl having hydroxy and naphthyloxy and the more preferred one may be 2-[2-hydroxy-3-(1-naphthyloxy)-propylamino]ethyl.

"imido(lower)alkyl" is exemplified by e.g. phthalimidomethyl, 2-phthalimidoethyl, 1-(1,2-cyclohexanedicarboximido)ethyl, 2-succinimidopropyl, 3-phthalimidobutyl, 2-(1,2-cyclohexandicarboximido)-1,1-dimethylethyl, 5-phthalimidopentyl, or 1-phthalimidohexyl, the more preferred one may be imido(C_1-C_4)alkyl and the most preferred one may be 2-phthalimidoethyl.

Suitable "cyano(lower)alkyl" may include cyanomethyl, 1-cyanoethyl, 2-cyanoethyl, 3-cyanopropyl, 2-cyanobutyl, 4-cyanobutyl, 2-cyano-1,1-dimethylethyl, 4-cyanopentyl, 5-cyanopentyl, or 6-cyanohexyl, in which the preferred one may be cyano(C_1-C_6)alkyl and the most preferred one may be cyanomethyl, 2-cyanoethyl, 3-cyanopropyl, 4-cyanobutyl, 5-cyanopentyl and 6-cyanohexyl.

Suitable "cyano(higher)alkyl" may include 7-cyanoheptyl, 8-cyanooctyl, 4-cyanooctyl, 8-cyano-3-methylheptyl, 9-cyanononyl, 1-cyanononyl, 10-cyanodecyl, 8-cyanoundecyl, 12-cyanododecyl, 11-cyano-4-methylundecyl, 13-cyanotridecyl, 6-cyanotetradecyl, 15-cyanopentadecyl, 12-cyanohexadecyl, 17-cyanoheptadecyl, 4-cyanooctadecyl, 19-cyanononadecyl, 1-cyano-12-ethylheptadecyl, 20-cyanoicosyl, and the like, in which the preferred one may be cyano (C_7-C_{16})alkyl and the more preferred one may be 7-cyanoheptyl, 8-cyanooctyl, 9-cyanononyl, 10-cyanodecyl and 12-cyanododecyl.

Suitable "lower alkyl" may be a straight or branched one such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, or hexyl.

Suitable "C_2-C_4 alkenyl" may be a straight or branched one such as vinyl, allyl, 2-butenyl, or 2-methyl-2-propenyl, in which the preferred one may be vinyl.

Suitable "lower alkyl" in lower alkyl having the heterocyclic group, as defined in claim 1 can be referred to the ones as exemplified before, and the preferred one may be methyl, ethyl, propyl, butyl, pentyl and hexyl.

Suitable "higher alkyl" in "higher alkyl having tetrazolyl" may include heptyl, octyl, 3-methylheptyl, nonyl, 2,6-dimethylheptyl, decyl, undecyl, dodecyl, 4-methyldodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, 12-ethylheptadecyl, or icosyl, in which the preferred one may be (C_7-C_{16})alkyl, and the more preferred one may be heptyl, octyl, nonyl, decyl, and dodecyl. The heterocyclic group in the lower alkyl having the heterocyclic group, in which heterocyclic group may have 1 to 3 suitable substituent(s) as defined in claim 1 and the higher alkyl having tetrazolyl are enumerated as follows: pyridyl, tetrazolyl (e.g., 1H-tetrazolyl, and 2H-tetrazolyl), piperidyl (e.g. piperidino, etc.), and piperazinyl; morpholinyl, oxazolidinyl (e.g. 1,3-oxazolidinyl) and tetrahydropyranyl (e.g. tetrahydro-2H-pyran-2-yl).

The examples of the heterocyclic group in the lower alkyl having the heterocyclic group, in which the heterocyclic group may have 1 to 3 suitable substituent(s) as defined in claim 1 and the higher alkyl having tetrazolyl are enumerated further as pyridyl, tetrazolyl, piperidyl, piperazinyl, morpholinyl, oxazolidinyl and tetrahydropyranyl; and the preferred one may be 4-pyridyl, 1H-tetrazol-5-yl, piperidino, 1-piperazinyl, morpholino, 1,3-oxazolidin-5-yl and tetrahydro-2H-pyran-2-yl.

The heterocyclic group attached to lower alkyl thus explained may have 1 to 3 suitable substituent(s) selected from hydroxy(lower)alkyl (e.g. hydroxymethyl, 2-hydroxyethyl, 1-hydroxypropyl, 4-hydroxybutyl, 2-hydroxy-1,1-dimethylethyl, 3-hydroxypentyl, or 6-hydroxyhexyl), phenyl which may have lower alkoxy (e.g. phenyl, 2-methoxyphenyl, 2-methoxynaphthyl, 3-ethoxyphenyl, 4-propoxyphenyl, 2-butoxyphenyl, 3-t-butoxyphenyl, 4-pentyloxyphenyl, or 2-hexyloxyphenyl), and oxo, in which preferred suitable substituent(s) may be hydroxy(C_1-C_4)alkyl, phenyl having (C_1-C_4)alkoxy and oxo, and the more preferred one may be 2-hydroxyethyl, 2-methoxyphenyl and oxo.

"Dihydrochromenyl" may be 3,4-dihydro-2H-chromen-4-yl, which may have 1 to 4 suitable substituent(s) selected from the aforesaid lower alkyl, hydroxy, and cyano in which the preferred one may be (C_1-C_4)alkyl, hydroxy and cyano, and the most preferred one may be methyl, hydroxy and cyano.

Suitable "phenyl(lower)alkyl" may include mono- or di- or tri- phenyl(lower)alkyl (e.g. benzyl, phenethyl, 2-phenylpropyl, 4-phenylbutyl, 2-phenyl-1,1-dimethylethyl, 1-phenylpentyl, 6-phenylhexyl, benzhydryl, and trityl) in which the preferred one may be phenyl(C_1-C_4)alkyl and the most preferred one may be benzyl.

Suitable tetrazolyl(lower)alkyl may be 1H-tetrazol-5-ylmethyl, 2-(1H-tetrazol-5-yl)ethyl, 3-(1H-tetrazol-5-yl)propyl, 4-(1H-tetrazol-5-yl)butyl, 2-(2H-tetrazol-2-yl)-1,1-dimethylethyl, 4-(1H-tetrazol-1-yl)pentyl, 5-(1H-tetrazol-5-yl)pentyl,

or 6-(1H-tetrazol-5-yl)hexyl, in which the preferred one may be (1H-tetrazol-5-yl)methyl, 2-(1H-tetrazol-5-yl)ethyl, 3-(1H-tetrazol-5-yl)propyl, 4-(1H-tetrazol-5-yl)butyl, 5-(1H-tetrazol-5-yl)pentyl and 6-(1H-tetrazol-5-yl)hexyl.

Suitable "tetrazolyl(higher)alkyl")alkyl" may be 7-(1H-tetrazol-5-yl)heptyl, 8-(1H-tetrazol-5-yl)octyl, 4-(1H-tetrazol-1-yl)octyl, 8-(1H-tetrazol-5-yl)-3-methylheptyl, 9-(1H-tetrazol-5-yl)nonyl, 1-(1H-tetrazol-1-yl)nonyl, 10-(1H-tetrazol-5-yl)decyl, 8-(1H-tetrazol-5-yl)undecyl, 12-(1H-tetrazol-5-yl)dodecyl, 11-(1H-tetrazol-5-yl)-4-methylundecyl, 13-(1H-tetrazol-5-yl)tridecyl, 6-(1H-tetrazol-5-yl)tetradecyl, 15-(1H-tetrazol-5-yl)-pentadecyl, 12-(1H-tetrazol-5-yl)hexadecyl, 17-(1H-tetrazol-1-yl)heptadecyl, 4-(1H-tetrazol-5-yl)octadecyl, 19-(1H-tetrazol-5-yl)nonadecyl, 1-(1H-tetrazol-1-yl)-12-ethylheptadecyl, or 20-(1H-tetrazol-5-yl)icosyl, in which the preferred one may be tetrazolyl(C_7-C_{16})alkyl and the more preferred one may be 7-(1H-tetrazol-5-yl)heptyl, 8-(1H-tetrazol-5-yl)octyl, 9-(1H-tetrazol-5-yl)nonyl, 10-(1H-tetrazol-5-yl)decyl and 12-(1H-tetrazol-5-yl)dodecyl.

Suitable "lower alkyl" moiety in "lower alkyl having a group of the formula :

"

as defined in the claims can be referred to the ones as exemplified before for "lower alkyl".

Suitable "carboxy(lower)alkyl" can be referred to the ones as exemplified before for "carboxy(lower)alkyl" moiety of "carboxy(lower)alkylamino(lower)alkyl".

Suitable "lower alkyl having hydroxy and naphthyloxy" may include 1-(1-naphthyloxy)-1-hydroxymethyl, 2-hydroxy-3-(1-naphthyloxy)propyl, 4-hydroxy-1-(2-naphthyloxy)butyl, 1-hydroxy-5-(1-naphthyloxy)pentyl, and 2-hydroxy-4-(2-naphthyloxy)hexyl.

Suitable "lower alkylamino having hydroxy and naphthyloxy" may include 1-(1-naphthyloxy)-1-hydroxymethylamino, 1-hydroxy-2-phenoxyethylamino, 2-hydroxy-3-(1-naphthyloxy)propylamino, 4-hydroxy-3-(p-tolyloxy)butylamino, 4-hydroxy-1-(2-naphthyloxy)butylamino, 1-hydroxy-5-(1-naphthyloxy)pentylamino, and 2-hydroxy-4-(2-naphthyloxy)hexylamino.

Suitable "hydroxy(lower)alkyl" can be referred to the ones as exemplified before.

Suitable "lower alkyl having epoxy and naphthyloxy" may include 1,2-epoxy-2-(1-naphthyloxy)ethyl, 1,2-epoxy-3-(1-naphthyloxy)propyl, 3,4-epoxy-3-(p-tolyloxy)butyl, 1,2-epoxy-5-(1-naphthyloxy)pentyl, and 2,3-epoxy-4-(2-naphthyloxy)hexyl.

Suitable "lower alkylamino" can be referred to the ones as exemplified before for "lower alkylamino" moiety of "lower alkylamino(lower)alkyl".

Suitable "carboxy(lower)alkylamino" can be referred to the ones as exemplified before for "carboxy(lower)alkylamino" moiety of "carboxy(lower)alkylamino(lower)alkyl".

Suitable "halogen" may include fluoro, chloro, bromo and iodo.

Suitable "halo(lower)alkyl" may include bromomethyl, 1-chloroethyl, 2-fluoroethyl, 3-iodopropyl, 2-bromobutyl, 4-chlorobutyl, 2-bromo-1,1-dimethylethyl, 4-bromopentyl, 5-bromopentyl, and 6-bromohexyl, in which the preferred one may be halo(C_3-C_6)alkyl.

Suitable "arylsulfonyl" may include phenylsulfonyl, tolylsulfonyl, and naphthylsulfonyl and said "arylsulfonyl" may have one or more (preferably 1 to 3) suitable substituent(s) such as aforesaid lower alkoxy, or aforesaid halogen.

Suitable "a leaving group" may include di(lower)alkylamino (e.g. dimethylamino, diethylamino, N-ethylpropylamino, dibutylamino, and N-pentylhexylamino), tri(lower)alkylammonio (e.g. trimethylammonio), lower alkoxy as mentioned above, halogen as mentioned above, lower alkylthio (e.g. methylthio, ethylthio, propylthio, butylthio, pentylthio, and hexylthio), acyloxy such as lower alkanoyloxy (e.g. acetoxy), sulfonyloxy like lower alkyl sulfonyloxy (e.g. mesyloxy), arylsulfonyloxy (e.g. phenylsulfonyloxy, and tosyloxy).

Suitable "anion" may be formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, chloride, bromide, iodide, sulfate, or phosphate.

The processes for preparing the object compounds of the present invention are explained in detail in the following.

Process 1

The compound (I) or a salt thereof can be prepared by reacting the compound (II) or a salt thereof with the compound (III) or a salt thereof.

Suitable salt of the compound (II) can be referred to an acid addition salt as exemplified for the compound (I).

Suitable salt of the compound (III) can be referred to the ones as exemplified for the compound (I).

The present reaction may be carried out in a solvent such as water, phosphate buffer, acetone, chloroform, acetonitrile nitrobenzene, methylene, chloride, ethylene chloride, formamide, N,N-dimethylformamide, methanol, ethanol, sec-butanol, amyl alcohol, diethyl ether, dioxane, tetrahydrofuran, dimethyl sulfoxide, or any other organic solvent

which does not adversely affect the reaction, preferably in ones having strong polarities. Among the solvents, hydrophilic solvents may be used in a mixture with water. When the compound (III) is in liquid, it can also be used as a solvent. The reaction is preferably conducted in the presence of a base, for example, inorganic base such as alkali metal hydroxide, alkali metal carbonate, alkali metal bicarbonate, alkali metal hydride, and organic base such as trialkylamine.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating.

The present reaction is preferably carried out in the presence of alkali metal halide [e.g. sodium iodide, and potassium iodide], alkali metal thiocyanate [e.g. sodium thiocyanate, and potassium thiocyanate.

Process 2

The compound (Ib) or a salt thereof can be prepared by subjecting the compound (Ia) or a salt thereof to elimination reaction of amino protective group.

Suitable salts of the compounds (Ia) and (Ib) can be referred to acid addition salts as exemplified for the compound (I).

This reaction is carried out in accordance with a conventional method such as hydrolysis, or reduction.

The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid.

Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g. sodium, and potassium], an alkaline earth metal [e.g. magnesium, and calcium], the hydroxide or carbonate or bicarbonate thereof, trialkylamine [e.g. trimethylamine, and triethylamine], hydrazine, picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, or 1,8-diazabicyclo[5.4.0]undec-7-ene.

Suitable acid may include an organic acid [e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, and trifluoroacetic acid] and an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, and hydrogen bromide].

The elimination using Lewis acid such as trihaloacetic acid [e.g. trichloroacetic acid, and trifluoroacetic acid] is preferably carried out in the presence of cation trapping agents [e.g. anisole, and phenol].

The reaction is usually carried out in a solvent such as water, an alcohol [e.g. methanol, and ethanol], methylene chloride, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent. The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

The reduction method applicable for the elimination reaction may include chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g. tin, zinc, and iron] or metallic compound [e.g. chromium chloride, and chromium acetate] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, and hydrobromic acid].

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, and platinum wire], palladium catalysts [e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, and palladium on barium carbonate], nickel catalysts [e.g. reduced nickel, nickel oxide, and Raney nickel], cobalt catalysts [e.g. reduced cobalt, and Raney cobalt], iron catalysts [e.g. reduced iron, and Raney iron], copper catalysts [e.g. reduced copper, Raney copper, and Ullman copper].

The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, N,N-dimethylformamide, or a mixture thereof. Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, and other conventional solvent such as diethyl ether, dioxane, and tetrahydrofuran, or a mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to warming.

Process 3

The compound (Ic) or a salt thereof can be prepared by reacting the compound (Ib) or a salt thereof with the compound (IV) or a salt thereof.

Suitable salts of the compounds (Ic) and (IV) can be referred to the ones as exemplified for the compound (I).

This reaction can be carried out in a similar manner to that of Process 1 mentioned in the above, and therefore the reaction mode and reaction conditions [e.g. base, acid, catalyst, solvent, and reaction temperature] of this reaction are to be referred to those as explained in Process 1.

Process 4

The compound (Ie) or a salt thereof can be prepared by subjecting the compound (Id) or a salt thereof to elimination reaction of carboxy protective group.

Suitable salt of the compound (Id) can be referred to acid addition salt as exemplified for the compound (I).

Suitable salt of the compound (Ie) can be referred to the ones as exemplified for the compound (I).

This reaction can be carried out in a hydrolysis condition of Process 2 mentioned in the above, and therefore the reaction mode and reaction conditions [e.g. base, acid, catalyst, solvent, and reaction temperature] of this reaction are to be referred to those as explained in Process 2.

Process 5

The compound (If) or a salt thereof can be prepared by reacting the compound (Ib) or a salt thereof with the compound (V).

Suitable salt of the compound (If) can be referred to an acid addition salt as exemplified for the compound (I).

This reaction can be carried out in a similar manner to that of Process 1 mentioned in the above, and therefore the reaction mode and reaction conditions [e.g. base acid, catalyst, solvent, and reaction temperature] of this reaction are to be referred to those as explained in Process 1.

Process 6

The compound (Ig) or a salt thereof can be prepared by reacting the compound (VI) or its reactive derivative at hydroxy group or a salt thereof with the compound (VII) or a salt thereof.

Suitable reactive derivative at hydroxy group of the compound (VI) may be the derivative obtained by reacting the compound (VI) with thionyl halide (e.g. thionyl chloride), phosphoryl halide (e.g. phosphoryl chloride), sulfonyl halide (e.g. tosyl chloride, and mesyl chloride).

Suitable salt of the compound (VI) can be referred to an acid addition salt as exemplified for the compound (I).

Suitable salts of the compounds (Ig) and (VII) can be referred to the ones as exemplified for the compound (I).

This reaction can be carried out in a similar manner to that of Process 1 mentioned in the above, and therefore the reaction mode and reaction conditions [e.g. base, acid, catalysts, solvent, and reaction temperature] or this reaction are to be referred to those as explained in Process 1.

Process 7

The compound (Ii) or a salt thereof can be prepared by subjecting the compound (Ih) or a salt thereof to formation reaction of tetrazolyl group.

Suitable salts of the compounds (Ih) and (Ii) can be referred to acid addition salts as exemplified for the compound (I).

The formation reaction of tetrazolyl group of this step can be carried out by reacting the compound (Ih) or a salt thereof with an azido compound such as alkali metal azide (e.g. sodium azide) or the like.

The reaction is usually carried out in a solvent such as N-methylpyrrolidone, toluene, dimethyl sulfoxide, acetone, or any other solvent which does not adversely influence the reaction.

The reaction can be carried out in the presence of a base such as tri(lower)alkylamine (e.g. trimethylamine, and triethylamine).

The reaction temperature is not critical and the reaction can be carried out under warming or heating.

Process 8

The compound (Ij) or a salt thereof can be prepared by subjecting the compound (VI) or a salt thereof to dehydration reaction.

Suitable salt of the compound (Ij) can be referred to an acid addition salt as exemplified for the compound (I).

The reaction can be carried out by the method disclosed in Example mentioned later or a similar manner thereto.

Process 9

The compound (Ih) or a salt thereof can be prepared by subjecting the compound (VIII) or a salt thereof to cyanation reaction.

The suitable salt of the compound (VIII) can be referred to acid addition salts as exemplified for the compound (I).

The cyanation reaction of this step can be carried out by reacting the compound (VIII) or a salt thereof with alkali metal cyanide (e.g. sodium cyanide).

The reaction can be carried out in a similar manner to that of Process 1 mentioned in the above, and therefore the reaction mode and reaction conditions of this reaction are to be referred to those as explained in Process 1.

The processes for preparing the starting compound (II) or a salt thereof are explained in detail in the following.

Process A

Step 1 to 3

The reactions of these steps can be carried out by the methods disclosed in Preparations mentioned later or the similar manners thereto.

Step 4

The compound (XVI) or a salt thereof can be prepared by reacting the compound (XIV) or a salt thereof with the compound (XV).

Suitable salts of the compounds (XIV) and (XVI) can be referred to acid addition salts as exemplified for the compound (I).

The reaction is usually carried out in a solvent such as water, methylene chloride, ethylene chloride, N,N-dimethylformamide or any other solvent which does not adversely influence the reaction or a mixture thereof.

The reaction can be carried out in the presence of a base such as alkali metal hydroxide (e.g. sodium hydroxide, and potassium hydroxide), ar(lower)alkyltri(lower)alkylammonium halide (e.g. benzyltrimethylammonium chloride).

The reaction temperature is not critical and the reaction is usually carried out under cooling, at room temperature or under warming.

Step 5

The compound (II) or a salt thereof can be prepared by subjecting the compound (XVI) or a salt thereof to hydrolysis.

Suitable salt of the compound (XVI) can be referred to an acid addition salt as exemplified for the compound (I).

This reaction can be carried out in a hydrolysis condition of Process 2 mentioned in the above, and therefore the reaction mode and reaction conditions [e.g. base, acid, catalyst, solvent, and reaction temperature] of this reaction are to be referred to those as explained in Process 2.

In order to show the usefulness of the compound (I) of the present invention, the pharmacological test result of the representative compound of the present invention is shown in the following.

Test 1. Activity of Increasing the Renal Blood Flow

[I] Test Method

Adult Beagle dogs of either sex, weighing 8-15 kg, were used. Under anesthesia with pentobarbital sodium (35 mg/kg i.p.), the trachea was intubated for artificial respiration. Catheters were placed in an femoral vein for drug administration.

A short segment of left renal artery was exposed by a flank incision and cleared of adhering tissue to accommodate positioning of an electromagnetic flow probe. Renal blood flow was measured by connecting the flow probe to an flowmeter.

[II] Test Compound

3-[2-(2-Dimethylaminoethyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine hydrochloride

[III] Test Result

Dose (mg/kg)	Increasing % of Renal Blood Flow
0.32	+ 26.0

Test 2. Test on Diuretic Activity

[I] Test Method

Male JCL:SD strain rats aged 6 weeks and weighing about 200 g were used after starving for 18 hours. Immediately after oral dosing with the test compound suspended in 0.5% methylcellulose (0.5% MC), the animals were given 20 ml/kg physiological saline orally. The rats were housed by threes in a metabolism cage. The urine was collected for 6 hours. Urinary electrolyte (Na^+) was measured with a Stat/Ion^R System (Technichon). The tests were conducted in 3 groups of 3 animals each.

[II] Test Compound

3-[2-{3-(1H-Tetrazol-5-yl)propyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

[III] Test Result

The urine volume and urinary electrolyte (Na^+) (%, control = 100%) were as follows.

Dose (mg/kg)	Urine Volume (%)	Na^+ (%)
10.0	250	316

Test 3. Test on Adenosine Antagonism

[I] Test Method

Male Hartley strain guinea-pigs, weighing 500-650 g, were killed by bleeding and the hearts were removed.

An atrial strip was removed and suspended in an organ bath containing 50 ml of Tyrode's solution maintained at 27-30°C and aerated with a gas mixture of 95% O_2 - 5% CO_2. The atrium was connected to a strain gauge under an initial tension of 0.4-0.6 g. After constant motility had been obtained, the test compound and the adenosine (1 X 10^{-5} M) were added. The negative inotropic activity of the adenosine was compared in the absence or presence of the test compound and then the adenosine antagonistic activities were measured.

[II] Test Compound

The same compound as used in Test 2

[III] Test Result

The negative inotropic activity of the adenosine was as follows.

	Inhibition (%)
In the absence of Test Compound	70.4 ± 4.1
In the presence of Test Compound (dose : 1 x 10^{-8}M)	1.0 ± 0.6**
(mean ± S.E.)	

** P<0.01 (vs absence of Test Compound)

Test 4. Test on Protective effect in glycerol-induced renal toxicity in rats

[I] Test Method

Male Sprague-Dawley rats (weighing 290 - 310 g) were fasted and dehydrated for 24 hours, renal toxicity was produced by intramuscular injection of 25% V/V glycerol in sterile saline (0.9% W/V NaCl), 10 ml/kg body weight. One hour before the injection of glycerol, rats were given a single oral dose of either test compound (1 mg/kg) or vehicle (5 ml/kg of 0.5% methyl cellulose). Twenty-four hours after glycerol injection, each rat was anesthetized with ether and blood sample was taken from abdominal aorta for the determination of plasma creatinine and BUN (blood urine nitrogen).

[II] Test Compound

The same compound as used in Test 2

[III] Test Result

Group	BUN (mg/dl) (mean ± S.E.)	Plasma creatinine (mg/dl) (mean ± S.E.)
vehicle	63.6 ± 10.2	2.15 ± 0.34
Test Compound (1 mg/kg)	29.2** ± 5.9	1.09** ± 0.10

** P<0.01

The pharmaceutical composition of this invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains the pyrazolopyridine compound (I) or a pharmaceutically acceptable salt thereof, as an active ingredient in admixture with an organic or inorganic carrier or excipient suitable for rectal, pulmonary (nasal or buccal inhalation), nasal, ocular, external (topical), oral or parenteral (including subcutaneous, intravenous and intramuscular) administrations or insufflation. The active ingredient may be compounded, for example, with the usual non toxic, pharmaceutically acceptable carriers for tablets, pellets, troches, capsules, suppositories, creams, ointments, aerosols, powders for insufflation, solutions, emulsions, suspensions, and any other form suitable for use. And, if necessary, in addition, auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. The pyrazolopyridine compound (I) or a pharmaceutical acceptable salt thereof is/are included in the pharmaceutical composition in an amount sufficient to produce the desired aforesaid pharmaceutical effect upon the process or condition of diseases.

For applying the composition to human being or animals, it is preferable to apply it by intravenous, intramuscular, pulmonary, or oral administration, or insufflation. While the dosage of therapeutically effective amount of the pyrazolopyridine compound (I) varies from and also depends upon the age and condition of each individual patient to be treated, in the case of intravenous administration, a daily dose of 0.01 - 100 mg of the pyrazolopyridine compound (I) per kg weight of human being or animals, in the case of intramuscular administration, a daily dose of 0.1 - 100 mg of the pyrazolopyridine compound (I) per kg weight of human being or animals, in case of oral administration, a daily dose of 0.5 - 100 mg of the pyrazolopyridine compound (I) per kg weight of human being or animals is generally given for the prevention and/or treatment of aforesaid diseases.

The following Preparations and Examples are given for the purpose of illustrating the present invention in more detail.

Preparation 1

A mixture of 3,6-dichloropyridazine (50 g), sodium benzenesulfinate dihydrate (100 g), benzyltrimethylammonium chloride (62.3 g), and 1,4-dioxane (335 ml) was stirred for 3 hours at 100°C. After being cooled to room temperature, aqueous solution of sodium hydroxide (510 ml) was added to the mixture, and the mixture was stirred for 0.5 hour at 100°C. The reaction mixture was cooled in a water bath and acidified with 36% hydrochloric acid (35 ml). The precipitate formed was collected, washed well with water, and dried to give 6-phenylsulfonyl-3-oxo-2,3-dihydropyridazine (54.7 g).

mp : 189-191°C
IR (Nujol) : 1680, 1650, 1370, 1160 cm^{-1}
NMR (DMSO-d_6, δ) : 7.12 (1H, d, J=10Hz), 7.6-7.9 (3H, m), 7.9-8.1 (3H, m) 13.85 (1H, broad s)
MASS m/z : 236

Anal. Calcd. for $C_{10}H_8N_2O_3S$:				
Found :	C 50.84, C 51.10,	H 3.41, H 3.33,	N 11.86, N 11.70,	S 13.57 (%) S 13.23 (%)

Preparation 2

To stirring phosphorous oxychloride (87 ml) at 80°C was added four 2.0 g portions of 6-phenylsulfonyl-3-oxo-2,3-dihydropyridazine every 30 minutes. After additional two 1.0 g portions were added with stirring, the reaction mixture

was slowly poured into ice-water over 1 hour to form the precipitate, which was collected, washed well with water, and dried to give 6-chloro-3-phenylsulfonylpyridazine (8.4 g).

An analytical sample was prepared by recrystallization from a mixture of diisopropyl ether and acetone (3:1).

mp : 142-144°C
IR (Nujol) : 3100, 3050, 1580, 1540, 1370, 1180 cm^{-1}
NMR ($CDCl_3$, δ) : 7.5-7.7 (3H, m), 7.74 (1H, d, J=9Hz), 8.0-8.2 (2H, m), 8.25 (1H, d, J=9Hz)
MASS m/z : 192 (M^+ - 62), 190 (M^+ - 64), 155

Anal. Calcd. for $C_{10}H_7ClN_2O_2S$:				
Found :	C 47.16, C 47.09,	H 2.77, H 2.65,	N 11.00, N 10.71,	S 12.59 (%) S 12.12 (%)

Preparation 3

To a solution of 6-chloro-3-phenylsulfonylpyridazine (8.4 g) bis(triphenylphosphine)palladium(II) chloride (98%; 0.24 g), copper(I) iodide (95%; 63 mg), and triethylamine (9.2 ml) in N,N-dimethylformamide (84 ml) was added phenylacetylene (4.7 ml), and the mixture was stirred for 0.5 hour at 80°C. After being cooled to room temperature, water (168 ml) was added to the reaction mixture. The precipitate formed was collected, washed with water, and dried. Recrystallization of the crude product from a mixture of diisopropyl ether and acetone (2:1) gave 6-(2-phenylethynyl)-3-phenylsulfonylpyridazine (5.5 g). After the mother liquor was concentrated in vacuo, the residue was triturated with acetone. The precipitate was collected and dried to give a second crop of the pure material (2.0 g).

mp : 179-181°C
IR (Nujol) : 2200, 1370, 1180 cm^{-1}
NMR ($CDCl_3$, δ) : 7.3-7.5 (3H, m), 7.5-7.7 (5H, m), 7.81 (1H, d, J=9Hz), 8.1-8.2 (2H, m), 8.25 (1H, d, J=9Hz)
MASS m/z : 256 (M^+ - 64)

Anal. Calcd. for $C_{18}H_{12}N_2O_2S$:				
Found :	C 67.48, C 67.53,	H 3.78, H 3.69,	N 8.74, N 8.23,	S 10.00 (%) S 9.71 (%)

Preparation 4

A two-phase mixture of 6-(2-phenylethynyl)-3-phenylsulfonylpyridazine (23.3 g), 1-aminopyridinium iodide (90%; 26.9 g), sodium hydroxide (11.6 g), and benzyltrimethylammonium chloride (1.35 g) in a mixture of methylene chloride (233 ml) and water (233 ml) was stirred for 2 hours at room temperature. Water (233 ml) was added to the reaction mixture, and the mixture was acidified with 36% hydrochloric acid (20 ml). The organic layer was separated, washed twice with water and once with sodium chloride aqueous solution, dried over anhydrous magnesium sulfate, and concentrated. The residue was washed with hot ethanol (300 ml) to give 3-(3-phenylsulfonylpyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyridine (20.8 g). An analytical sample was prepared by recrystallization from ethyl acetate.

mp : 192-194°C
IR (Nujol) : 1620, 1560, 1370, 1180 cm^{-1}
NMR ($CDCl_3$, δ) : 6.9-7.1 (1H, m), 7.3-7.5 (1H, m), 7.36 (1H, d, J=9Hz), 7.5-7.9 (8H, m), 7.93 (1H, d, J=9Hz), 8.1-8.2 (2H, m), 8.5-8.6 (2H, m)
MASS m/z : 412, 411 (M^+ - 1)

Anal. Calcd. for $C_{23}H_{16}N_4O_2S$:				
Found :	C 66.98, C 67.31,	H 3.91, H 3.83,	N 13.58, N 13.34,	S 7.77 (%) S 7.95 (%)

Preparation 5

A mixture of 3-(3-phenylsulfonylpyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyridine (20.0 g), sodium hydroxide solution (80 ml; containing 7.8 g of sodium hydroxide), and 1,4-dioxane (40 ml) was stirred for 2 hours under reflux. After being cooled to room temperature, the reaction mixture was acidified with 36% hydrochloric acid (15 ml). The precipitate formed was collected, washed with three 25 ml portions of water, and dried to give 3-(3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyridine (16.0 g). An analytical sample was prepared by recrystallization from ethyl acetate.

mp : 229-230°C
IR (Nujol) : 1680, 1630 cm^{-1}
NMR (DSMO-d_6, δ) : 6.84 (1H, d, J=10Hz), 7.12 (1H, d, J=10Hz), 7.0-7.1 (1H, m), 7.3-7.7 (6H, m), 7.86 (1H, broad d, J=9Hz), 8.82 (1H, broad d, J=7Hz), 13.19 (1H, broad s)
MASS m/z : 288, 287 (M^+ - 1)

Anal. Calcd. for $C_{17}H_{12}N_4O$:			
Found :	C 70.82, C 70.93,	H 4.20, H 4.18,	N 19.43 (%) N 19.38 (%)

Preparation 6

To an ice-cooled solution of 3-(3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyridine (2.0 g) in N,N-dimethylformamide (20 ml) was added portionwise sodium hydride (60% dispersion in mineral oil; 0.31 g). After addition was finished, the mixture was stirred for 15 minutes in an ice-bath. To this mixture was added 4-chlorobutyl acetate (1.1 g), and the reaction mixture was stirred for 24 hours at room temperature, and then for 36 hours at 70°C. After being cooled to room temperature, the reaction mixture was concentrated. The residue was partitioned between ethyl acetate and water.

The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with water and sodium chloride aqueous solution, dried over anhydrous magnesium sulfate, and concentrated. Purification of the residue by column chromatography on silica gel (using 3:1 mixture of chloroform and ethyl acetate as eluent) gave 3-[2-(4-acetoxybutyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo [1,5-a]pyridine (2.6 g). An analytical sample was prepared by recrystallization from diisopropyl ether.

mp : 102-103°C
IR (Nujol) : 1720, 1660 cm^{-1}
NMR ($CDCl_3$, δ) : 1.7-1.9 (2H, m), 1.9-2.2 (2H, m), 2.05 (3H, s), 4.16 (2H, t-like, J=ca. 6Hz), 4.31 (2H, t-like, J=ca. 6Hz), 6.77 (1H, d, J=10Hz), 6.8-7.0 (1H, m), 7.02 (1H, d, J=10Hz), 7.2-7.4 (1H, m), 7.4-7.5 (3H, m), 7.6-7.7 (2H, m), 7.9-8.0 (1H, m), 8.5-8.6 (1H, m)
MASS m/z : 402, 343, 287

Anal. Calcd. for $C_{23}H_{22}N_4O_3$:			
Found :	C 68.64, C 68.31,	H 5.51, H 5.48,	N 13.92 (%) N 13.76 (%)

Preparation 7

To an ice-cooled solution of 3-[2-(4-acetoxybutyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]-pyridine (2.6 g) in methanol (18 ml) was added a solution of sodium hydroxide (0.78 g) in methanol (8 ml). After addition was finished, the mixture was stirred for 15 minutes at room temperature. The reaction mixture was concentrated, and the residue was diluted with chloroform and water. The organic layer was separated and the aqueous layer was extracted twice with chloroform. The combined organic layers were washed with sodium chloride aqueous solution, dried over anhydrous magnesium sulfate, and concentrated.

Purification of the residue by column chromatography on silica gel (using a mixture of chloroform and methanol (25:1) as an eluent) gave 3-[2-(4-hydroxybutyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine (1.8 g). An analytical sample was prepared by recrystallization from toluene.

mp : 115-116°C
IR (Nujol) : 3400, 1660, 1630 cm^{-1}
NMR ($CDCl_3$, δ) : 1.6-1.8 (2H, m), 1.9-2.1 (2H, m), 2.41 (1H, broad s), 3.74 (2H, broad t), 4.32 (2H, t-like, J=ca. 7Hz), 6.76 (1H, d, J=9Hz), 6.7-7.0 (1H, m), 7.01 (1H, d, J=9Hz), 7.2-7.4 (1H, m), 7.4-7.5 (3H, m), 7.5-7.7 (2H, m), 7.9-8.0 (1H, m), 8.5-8.6 (1H, m)
MASS m/z : 289, 287 (M^+ - 73)

Anal. Calcd. for $C_{21}H_{20}N_4O_2$:			
Found :	C 69.98, C 70.25,	H 5.59, H 5.56,	N 15.55 (%) N 15.43 (%)

Preparation 8

To a suspension of 3-(3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyridine (1.0 g) and sodium hydride (60% 0.15 g) in N,N-dimethylformamide (10 ml) was added acetoxyethyl bromide (0.58 g) at 5°C, and the resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was poured into ice-water, and extracted twice with ethyl acetate. The extracts were combined, washed successively with 1N sodium hydroxide solution and sodium chloride aqueous solution, dried over magnesium sulfate, and then evaporated in vacuo. The residue was dissolved in 1,4-dioxane (12 ml) and a solution of sodium hydroxide (0.34 g) in water (1.5 ml) was added thereto. The reaction mixture was stirred at 60°C for 3 hours, and evaporated in vacuo. The residue was treated with water and extracted with chloroform. The extract was washed with sodium chloride aqueous solution, dried over magnesium sulfate, and then evaporated in vacuo. The residue was crystallized from ethyl acetate to afford 3-[2-(2-hydroxyethyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine (0.84 g).

mp : 185.5-187°C
IR (Nujol) : 3350, 1650, 1580, 1520, 1500 cm^{-1}
NMR ($CDCl_3$, δ) : 4.05 (2H, m), 4.30 (2H, d, J=4Hz), 6.70 (1H, d, J=10Hz), 6.82 (1H, td, J=7Hz and 1Hz), 7.00 (1H, d, J=10Hz), 7.15-7.60 (6H, m), 7.87 (1H, d, J=10Hz), 8.45 (1H, d, J=7Hz)
MASS : 332 (M^+)

Analysis Calcd. for $C_{19}H_{16}N_4O_2$:			
Found :	C 68.66, C 67.29,	H 4.85, H 5.05,	N 16.86 (%) N 16.42 (%)

Example 1

To a suspension of 3-(3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyridine (1.00 g) and sodium hydride (0.37 g, 60%) in N,N-dimethylformamide (5 ml) was added 4-(2-chloroethyl)morpholine hydrochloride (0.98 g). After being stirred for 1.5 hours at 70°C, the reaction mixture was poured into water (100 ml), and extracted twice with methylene chloride.
The combined extracts were washed with water, dried over anhydrous sodium sulfate and evaporated in vacuo. The residue was treated with a 20% solution of hydrogen chloride in ethanol (2 ml) to afford 3-[2-(2-morpholinoethyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine hydrochloride (0.72 g).

mp : 231.5-233°C
IR (Nujol) : 2325, 1670, 1590 cm^{-1}
NMR ($CDCl_3$, δ) : 3.18 (2H, m), 3.56 (4H, m), 3.75-4.0 (4H, m), 4.57 (2H, m), 6.93 (1H, d, J=10Hz), 7.13 (1H, t, J=6Hz), 7.14 (1H, d, J=10Hz), 7.40-7.68 (6H, m), 8.05 (1H, d, J=8Hz), 8.93 (1H, d, J=7Hz), 11.04 (1H, broad s)
MASS : 401 (M^+)

The following compounds (Examples 2 to 12) were obtained according to a similar manner to that of Example 1.

Example 2

3-[2-(2-Piperidinoethyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine hydrochloride

mp : 262.5-265°C
IR (Nujol) : 2495, 1660, 1595 cm^{-1}
NMR (DMSO-d_6, δ) : 1.78 (6H, m), 2.99 (2H, m), 3.45 (4H, m), 4.56 (2H, m), 6.95 (1H, d, J=9Hz), 7.07 (1H, t, J=17Hz), 7.15 (1H, d, J=9Hz), 7.40-7.65 (6H, m), 8.04 (1H, d, J=9Hz), 8.84 (1H, d, J=7Hz), 9.80 (1H, broad s)
MASS : 399 (M^+)

Example 3

3-[2-(2-Dimethylaminoethyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine hydrochloride

mp : 148.5-149.5°C
IR (Nujol) : 3520, 3450, 2600, 2370, 1640, 1570 cm^{-1}
NMR ($CDCl_3$, δ) : 2.92 (6H, s), 3.53 (2H, m), 4.77 (2H, m), 6.76 (1H, d, J=10Hz), 6.95 (1H, t, J=6Hz), 7.09 (1H, d, J=10Hz), 7.37-7.64 (6H, m), 8.15 (1H, d, J=8Hz), 8.53 (1H, d, J=7Hz), 13.10 (1H, broad s)

Example 4

3-[2-(3-Dimethylaminopropyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine hydrochloride

mp : 248-249°C
IR (Nujol) : 2400, 1655, 1590 cm^{-1}
NMR (DMSO-d_6, δ) : 2.15 (2H, m), 2.18 (2H, m), 2.75 (6H, s), 4.22 (2H, t, J=7Hz), 7.10 (1H, d, J=10Hz), 7.12 (1H, t, J=7Hz), 7.13 (1H, d, J=10Hz), 7.42-7.63 (6H, m), 7.99 (1H, d, J=12Hz), 8.83 (1H, d, J=8Hz), 10.1 (1H, broad s)

Example 5

3-[2-(2-Phthalimidoethyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

mp : 180-181°C (recrystallized from ethanol)
IR (Nujol) : 1760, 1710, 1660, 1630 cm^{-1}
NMR ($CDCl_3$, δ) : 4.1-4.3 (2H, m), 4.5-4.6 (2H, m), 6.70 (1H, d, J=10Hz), 6.8-6.9 (1H, m), 6.91 (1H, d, J=10Hz), 7.0-7.1 (1H, m), 7.3-7.7 (10H, m), 8.3-8.4 (1H, m)
MASS m/z : 461, 301, 287

Anal. Calcd. for $C_{27}H_{19}N_5O_3$:			
Found :	C 70.27, C 70.35,	H 4.15, H 4.20,	N 15.18 (%) N 15.18 (%)

Example 6

3-[2-(2-Cyanoethyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

mp : 170-170.5°C
IR (Nujol) : 1660, 1580 cm^{-1}
NMR ($CDCl_3$, δ) : 3.00 (2H, t, J=7Hz), 4.55 (2H, t, J=7Hz), 6.77 (1H, d, J=10Hz), 6.94 (1H, t, J=6Hz), 7.06 (1H, d, J=10Hz), 7.26-7.63 (6H, m), 8.14 (1H, d, J=9Hz), 8.53 (1H, d, J=6Hz)

Anal. Calcd.	C 70.36,	H 4.43,	N 20.52 (%)
Found	C 70.49,	H 4.41,	N 20.62 (%)

Example 7

3-[2-(3-Cyanopropyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

mp : 100-102°C
IR (Nujol) : 1655, 1580 cm^{-1}
NMR ($CDCl_3$, δ) : 2.2-2.4 (2H, m), 2.51 (2H, t, J=6.9Hz), 4.40 (2H, t, J=6.6Hz), 6.77 (1H, d, J=9.7Hz), 6.94 (1H, td, J=6.9Hz and J=1.3Hz), 7.06 (1H, d, J=9.7Hz), 7.3-7.7 (6H, m), 8.01 (1H, d, J=9.0Hz), 8.54 (1H, d, J=7.0Hz)
MASS : 355

Example 8

3-[2-(4-Cyanobutyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

mp : 140-142°C
IR (Nujol) : 1655, 1590 cm^{-1}
NMR (DMSO-d_6, δ) : 1.5-1.75 (2H, m), 1.8-2.0 (2H, m), 2.5 (2H, t, J=7.0Hz), 4.18 (2H, t, J=6.8Hz), 6.88 (1H, d, J=9.6Hz), 7.0-7.15 (2H, m), 7.35-7.65 (6H, m), 7.95 (1H, d, J=8.9Hz), 8.82 (1H, d, J=6.9Hz)

Example 9

3-(2-Benzyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyridine

mp : 182.5-183.5°C
IR (Nujol) : 1670, 1640, 1600, 1530 cm^{-1}
NMR ($CDCl_3$, δ) : 5.45 (2H, s), 6.76-7.63 (15H, m), 8.50 (1H, d, J=8Hz)
MASS : 378 (M^+)

Anal. Calcd.	C 76.17,	H 4.79,	N 14.80 (%)
Found	C 76.44,	H 4.84,	N 14.78 (%)

Example 10

3-[2-(2-oxo-1,3-oxazolidin-5-yl)methyl-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

mp : 165.5-166°C
IR (Nujol) : 3350-3400, 1715, 1690, 1645, 1580, 1520, 1495 cm^{-1}
NMR ($CDCl_3$, δ) : 3.28 (1H, q, J=6Hz), 3.49 (1H, m), 4.24 (1H, m), 4.44 (2H, d, J=5Hz), 5.45 (1H, broad s), 6.80 (1H, d, J=10Hz), 6.91 (1H, t, J=6Hz), 6.95 (1H, d, J=10Hz), 7.26-7.62 (6H, m), 8.00 (1H, d, J=10Hz), 8.54 (1H, d, J=7Hz)
MASS : 387 (M^+)

Anal. Calcd. for $C_{21}H_{17}N_5O_3$:			
	C 62.22,	H 4.69,	N 17.28 (%)
Found :	C 62.94,	H 4.91,	N 16.65 (%)

Example 11

3-[2-(4-Pyridylmethyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

mp : 165.5-166°C
IR (Nujol) : 1670, 1630, 1590, 1560, 1530 cm^{-1}
NMR ($CDCl_3$, δ) : 5.44 (2H, s), 6.80 (1H, d, J=10Hz), 6.90 (1H, t, J=6Hz), 7.05 (1H, d, J=10Hz), 7.19-7.68 (9H, m), 8.51 (1H, d, J=8Hz), 8.64 (2H, s)

MASS : 379 (M^+)

Anal. Calcd.	C 72.81,	H 4.52,	N 18.46 (%)
Found	C 73.19,	H 4.57,	N 18.54 (%)

Example 12

3-(2-Tetrahydro-2H-pyran-2-yl)-3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyridine

mp : 165-165.5°C
IR (Nujol) : 1660, 1630, 1590, 1530 cm^{-1}
NMR ($CDCl_3$, δ) : 1.52-1.88 (6H, m), 3.44 (1H, t, J=11Hz), 4.01 (2H, t, J=11Hz), 4.31 (2H, d, J=6Hz), 6.77 (1H, d, J=10Hz), 6.90 (1H, t, J=6Hz), 6.95 (1H, d, J=10Hz), 7.26-7.66 (6H, m), 8.11 (1H, d, J=10Hz), 8.52 (1H, d, J=6Hz)
MASS : 386 (M^+)

Anal. Calcd. for $C_{23}H_{22}N_3O_2$:			
	C 71.48,	H 5.47,	N 14.50 (%)
Found :	C 71.26,	H 5.67,	N 14.45 (%)

Example 13

A mixture of 3-[2-(2-phthalimidoethyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine (2.2 g), hydrazine monohydrate (2 ml), and ethanol (100 ml) was stirred for 1 hour under reflux. After being cooled to room temperature, the reaction mixture was concentrated, and the residue was partitioned between chloroform and water. The organic layer was separated, and extracted with 10% hydrochloric acid. The aqueous layer was washed twice with chloroform, neutralized with sodium hydroxide, and extracted three times with chloroform. The combined organic layers were washed with water and sodium chloride aqueous solution, dried over anhydrous magnesium sulfate, and concentrated to give 3-[2-(2-aminoethyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine (1.5 g). An analytical sample was prepared by recrystallization from ethyl acetate.

mp : >142°C
IR (Nujol) : 3380, 3300, 1660, 1630 cm^{-1}
NMR ($CDCl_3$, δ) : 1.47 (2H, broad s), 3.25 (2H, t-like, J=ca. 6Hz), 4.35 (2H, t-like, J=ca. 6Hz), 6.78 (1H, d, J=10Hz), 6.9-7.0 (1H, m), 7.04 (1H, d, J=10Hz), 7.3-7.4 (1H, m), 7.4-7.5 (3H, m), 7.6-7.7 (2H, m), 7.9-8.0 (1H, m), 8.5-8.6 (1H, m)
MASS m/z : 331, 302

Example 14

To an ice-cooled solution of 3-[2-(2-aminoethyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]-pyridine (1.5 g), triethylamine (1.5 ml), and N,N-dimethylformamide (15 ml) was added ethyl 2-bromoacetate (0.60 ml), and the mixture was stirred for 1 hour at room temperature. The reaction mixture was concentrated, and the residue was partitioned between chloroform and water. The organic layer was separated, washed with sodium chloride aqueous solution, dried over anhydrous magnesium sulfate, and concentrated.

Purification of the residue by column chromatography on silica gel (gradient elution, using 50:1 and 25:1 mixture of chloroform and methanol) gave 3-[2-{2-(ethoxycarbonylmethylamino)ethyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine (0.90 g).

mp : 212-214°C
IR (Nujol) : 2750, 2170, 2120, 2430, 1760, 1650, 1630 cm^{-1}
NMR ($CDCl_3$, δ) : 1.24 (3H, t, J=7Hz), 3.72 (2H, broad t, J=ca. 5Hz), 4.04 (2H, s), 4.21 (2H, q, J=7Hz), 4.79 (2H, broad t, J=ca. 5Hz), 6.79 (1H, d, J=10Hz), 6.8-6.9 (1H, m), 7.05 (1H, d, J=10Hz), 7.3-7.5 (4H, m), 7.6-7.7 (2H, m), 8.0-8.1 (1H, m), 8.4-8.5 (1H, m), 9.2-11.0 (1H, broad m)
MASS m/z : 417, 344, 315, 302

Example 15

To a solution of 3-[2-{2-(ethoxycarbonylmethylamino)-ethyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo-[1,5-a]pyridine (0.80 g) in ethanol (8 ml) was added a solution of sodium hydroxide (0.15 g) in water (4 ml) and the mixture was stirred for 0.5 hour at room temperature. The reaction mixture was concentrated and the residue was partitioned between water and ethyl acetate. The aqueous layer was separated, neutralized with 1N hydrochloric acid to give the precipitate, which was collected and purified by recrystallization from 50% aqueous ethanol to give 3-[2-{2-(carboxymethylamino)ethyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine (0.50 g).

mp : 230-232°C
IR (Nujol) : 3400, 1650, 1600 cm^{-1}
NMR ($CDCl_3$-CD_3OD=1:1, δ) : 3.19 (2H, broad t, J=ca. 6Hz), 3.22 (2H, s), 4.30 (2H, broad t, J=ca. 6Hz), 6.54 (1H, d, J=10Hz), 6.7-6.8 (1H, m), 6.83 (1H, d, J=10Hz), 7.1-7.2 (4H, m), 7.2-7.4 (2H, m), 7.7-7.8 (1H, m), 8.2-8.3 (1H, m)

Example 16

A mixture of 3-[2-(2-aminoethyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine (0.50 g), 1-[(2,3-epoxypropyl)oxy]naphthalene (0.36 g), and 1,4-dioxane (15 ml)-water (1.5 (ml) was stirred for 1 hour at 50°C, and then for 2 hours under reflux.

After being cooled to room temperature, the reaction mixture was concentrated, and the residue was purified by column chromatography on silica gel (gradient elution, using 50:1 and 25:1 mixture of chloroform and methanol) to give 3-[2-{2-{2-hydroxy-3-(1-naphthyloxy)propylamino}-ethyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo-[1,5-a]pyridine (0.49 g).

NMR ($CDCl_3$, δ) : 2.0-3.0 (2H, broad m), 2.9-3.1 (2H, m), 3.1-3.4 (2H, m), 4.0-4.3 (3H, m), 4.3-4.6 (2H, m), 6.7-6.8 (2H, m), 6.8-6.9 (1H, m), 6.98 (1H, d, J=10Hz), 7.0-7.5 (8H, m), 7.5-7.6 (2H, m), 7.7-7.8 (1H, m), 7.9-8.0 (1H, m), 8.1-8.2 (1H, m), 8.4-8.5 (1H, m)
MASS m/z : 532 (M^+ + 1)

Example 17

3-[2-{2-{2-Hydroxy-3-(1-naphthyloxy)propylamino}-ethyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo-[1,5-a]pyridine hydrochloride was obtained according to a conventional manner from the compound obtained in Example 16.

IR (Nujol) : 3300 (br), 1650, 1630 cm^{-1}
NMR (DMSO-d_6, δ) : 3.2-3.6 (4H, m), 4.1-4.2 (2H, m), 4.3-4.7 (1H, broad m), 4.59 (2H, broad m), 6.10 (1H, broad m), 6.94 (1H, d, J=10Hz), 6.9-7.0 (1H, m), 7.0-7.2 (1H, m), 7.13 (1H, d, J=10Hz), 7.3-7.6 (8H, m), 7.6-7.7 (2H, m), 7.8-7.9 (1H, m), 8.0-8.1 (1H, m), 8.2-8.3 (1H, m), 8.8-9.0 (1H, m), 9.0-9.3 (1H, broad m), 9.3-9.7 (1H, broad m)

Example 18

To an ice-cooled solution of 3-[2-(4-hydroxybutyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]-pyridine (1.5 g) in methylene chloride (15 ml) was added thionyl chloride (0.37 ml), and the solution was stirred for 0.5 hour at room temperature. Additional thionyl chloride (0.37 ml) was added to the mixture, and stirring was continued for 1 hour at room temperature followed by 1 hour at 40°C. Again, additional thionyl chloride (0.37 ml) was added, and the mixture was stirred for 1 hour under reflux. After being cooled to room temperature, the reaction mixture was concentrated to give the intermediate chloride compound.

To a solution of this intermediate chloride compound in sec-butyl alcohol (15 ml) was added 50% aqueous solution of dimethylamine (10 ml), and the mixture was stirred for 6 hours under reflux. After being cooled to room temperature, the reaction mixture was concentrated. The residue was dissolved in 1N hydrochloric acid and washed with ethyl acetate. The aqueous layer was separated, neutralized with sodium hydroxide, and extracted three times with chloroform. The combined organic layers were washed with saturated aqueous solution of sodium bicarbonate and sodium chloride aqueous solution, dried over anhydrous magnesium sulfate, and concentrated. Purification of the residue by column chromatography on silica gel (gradient elution, using 10:1 and 5:1 mixture of chloroform and methanol) gave 3-[2-(4-dimethylaminobutyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine.

This amine was dissolved in ethanol (5 ml) and treated with 20% solution of hydrogen chloride in ethanol (5 ml). The mixture was concentrated, and the residue was purified by recrystallization from a mixture of ethanol and diiso-

propyl ether to give 3-[2-(4-dimethylaminobutyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]-pyridine hydrochloride (0.89 g).

mp : 215 to 216°C
IR (Nujol) : 3100, 3050, 2400, 1660, 1630 cm^{-1}
NMR (DMSO-d_6, δ) : 1.6-2.0 (4H, broad m), 2.70 (6H, s), 3.08 (2H, broad s), 3.40 (1H, broad s), 4.1-4.2 (2H, broad m), 6.89 (1H, d, J=10Hz), 7.0-7.1 (1H, m), 7.10 (1H, d, J=10Hz), 7.4-7.5 (4H, m), 7.5-7.7 (2H, m), 7.97 (1H, m), 8.83 (1H, m)
MASS m/z : 387, 329

Example 19

A solution of 3-[2-(2-hydroxyethyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine (0.5 g) and thionyl chloride (0.13 ml) in methylene chloride (4 ml) was stirred at room temperature for 1 hour and evaporated in vacuo. To the residue was added dropwise a solution of l-(2-hydroxyethyl)piperazine (0.78 g) in amyl alcohol (5 ml), and the suspension was refluxed for 1.5 hours. The reaction mixture was evaporated in vacuo, and the residue was purified by column chromatography on silica gel using chloroform as eluent. The obtained oil was treated with a 20% solution of hydrogen chloride in ethanol to afford 3-[2-{2-{4-(2-hydroxyethyl)piperazin-1-yl}ethyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine dihydrochloride.

mp : 240-241.5°C
IR (Nujol) : 3400, 1660, 1590 cm^{-1}
NMR (DMSO-d_6, δ) : 3.42-3.79 (17H, m), 4.51 (2H, broad s), 6.90 (1H, d, J=10Hz), 7.08 (1H, t, J=6Hz), 7.10 (1H, d, J=10Hz), 7.40-7.70 (6H, m), 8.06 (1H, d, J=9Hz), 8.83 (1H, d, J=6Hz)

Anal. Calcd.	C 55.25,	H 6.08,	N 15.47 (%)
Found	C 55.16,	H 6.32,	N 15.18 (%)

Example 20

3-[2-{2-{4-(2-Methoxyphenyl)piperazin-1-yl}ethyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]-pyridine was obtained according to a similar manner to that of Example 19.

mp : 120-125°C
IR (Nujol) : 1680, 1585, 1525, 1500 cm^{-1}
NMR ($CDCl_3$, δ) : 2.84 (4H, m), 2.97 (2H, t, J=6Hz), 3.13 (4H, m), 3.87 (3H, s), 4.47 (2H, t, J=6Hz), 6.76 (1H, d, J=10Hz), 6.85-7.65 (12H, m), 8.05 (1H, d, J=10Hz), 8.53 (1H, d, J=7Hz)
MASS : 506 (M^+ - 1)

Anal. Calcd.	C 71.13,	H 5.97,	N 16.59 (%)
Found	C 71.17,	H 5.96,	N 16.58 (%)

Example 21

A mixture of 3-[2-(2-cyanoethyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine (0.35 g), sodium azide (0.20 g) and triethylamine hydrochloride (0.21 g) in N-methylpyrrolidone (10 ml) was stirred at 150°C for 4 hours under nitrogen atmosphere. The reaction mixture was poured into water (30 ml), acidified with 10% hydrochloric acid (5 ml), and extracted twice with ethyl acetate. The combined extracts were washed with water, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel using a mixture of chloroform and methanol (20:1) as an eluent. The fractions containing the object compound were combined and evaporated in vacuo. The residue was recrystallized from ethyl acetate to give 3-[2-{2-(1H-tetrazol-5-yl)ethyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]-pyridine (0.06 g).

mp : 230-232°C (decomp.)
IR (Nujol) : 1660, 1585 cm^{-1}

NMR ($CDCl_3$, δ) : 3.74 (2H, t, J=6Hz), 4.83 (2H, t, J=6Hz), 6.90 (1H, d, J=10Hz), 6.98 (1H, t, J=6Hz), 7.15 (1H, d, J=10Hz), 7.26-7.58 (6H, m), 7.96 (1H, d, J=7Hz), 8.56 (1H, d, J=6Hz), 11.96 (1H, broad s)

The following compounds (Examples 22 and 23) were obtained according to a similar manner to that of Example 21.

Example 22

3-[2-{3-(1H-Tetrazol-5-yl)propyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

mp : 215-217°C
IR (Nujol) : 1665, 1595 cm^{-1}
NMR (DMSO-d_6, δ) : 2.15-2.35 (2H, m), 3.00 (2H, t, J=7.6Hz), 4.26 (2H, t, J=6.9Hz), 6.86 (1H, d, J=9.7Hz), 7.05-7.15 (2H, m), 7.35-7.65 (6H, m), 7.96 (1H, d, J=8.9Hz), 8.82 (1H, d, J=6.9Hz)
MASS : 398, 355, 287

Anal. Calcd. for $C_{21}H_{18}N_8O$:			
Found :	C 63.31, C 63.03,	N 4.55, N 4.53,	H 28.12 (%) H 27.98 (%)

Example 23

3-[2-{4-(1H-Tetrazol-5-yl)butyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

mp : 213 to 214°C
IR (Nujol) : 1635, 1565 cm^{-1}
NMR (DMSO-d_6, δ) : 1.7-2.0 (4H, m), 2.97 (2H, t, J=6.7Hz), 4.19 (2H, m), 6.88 (1H, d, J=9.7Hz), 7.0-7.2 (2H, m), 7.35-7.5 (4H, m), 7.5-7.65 (2H, m), 7.89 (1H, d, J=8.9Hz), 8.82 (1H, d, J=6.9Hz)

Example 24

A solution of 3-[2-(2-hydroxyethyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine (0.5 g) and thionyl chloride (0.13 ml) in methylene chloride (4 ml) was stirred at room temperature for 1 hour and then evaporated in vacuo. To the residue were added, Triton B (2.04 g) and methylene chloride (4 ml). The reaction mixture was refluxed for 2 hours, poured into water (10 ml) and extracted with chloroform. The extract was washed with water, dried over magnesium sulfate and evaporated in vacuo.

The residue was purified by column chromatography on silica gel using chloroform as an eluent. The obtained oil was crystallized from a mixture of ethanol and ethyl acetate (1:1) to afford 3-(2-vinyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyridine.

mp : 187.5-188°C
IR (Nujol) : 1680, 1635, 1605 cm^{-1}
NMR ($CDCl_3$, δ) : 5.05 (1H, d, J=10Hz), 5.87 (1H, d, J=16Hz), 6.77 (1H, d, J=10Hz), 6.94-7.03 (2H, m), 7.26-7.66 (6H, m), 7.87 (1H, dd, J=16Hz and 10Hz), 8.10 (1H, d, J=10Hz), 8.55 (1H, d, J=7Hz)

Anal. Calcd.	C 72.60,	H 4.49,	N 17.83 (%)
Found	C 72.85,	H 4.62,	N 18.00 (%)

Example 25

A mixture of 3-(3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyridine (0.60 g), 2,2-dimethyl-3,4-epoxy-6-cyano-3,4-dihydro-2H-chromene (0.80 g), and 60% sodium hydride (0.16 g) in dimethylsulfoxide (6 ml) was stirred for 5 hours at 60°C, and then diluted with ethyl acetate. The mixture was washed with water (10 ml) and sodium chlroide aqueous solution (10 ml), dried over magnesium sulfate, and evaporated in vacuo. The residue was chromatographed on silica gel (10 g) with a mixture of n-hexane and ethyl acetate (2:1). The fractions containing the object compound

were combined and evaporated in vacuo. The residue was recrystallized from a mixture of ethyl acetate and diisopropyl ether to give 3-[2-(2,2-dimethyl-3-hydroxy-6-cyano-3,4-dihydro-2H-chromen-4-yl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine (0.51 g).

mp : 209-210°C
IR (Nujol) : 3330, 2220, 1670, 1600 cm^{-1}
NMR ($CDCl_3$, δ) : 1.41 (3H, s), 1.56 (3H, s), 3.32 (1H, d, J=5.8Hz), 4.25 (1H, m), 6.35 (1H, d, J=9.0Hz), 6.3-7.2 (7H, m), 7.4-7.6 (6H, m), 8.45 (1H, d, J=6.9Hz)
MASS : 489 (M^+), 456, 287

Anal. Calcd.	C 71.15,	H 4.74,	N 14.31 (%)
Found	C 70.97,	H 4.75,	N 14.06 (%)

Preparation 9

Potassium iodide (0.1 g) and 1,5-dibromopentane (4.6 g) were added to a suspension of 3-(3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyridine (2.88 g) and 60% sodium hydride (0.4 g) in N,N-dimethylformamide (40 ml). After being stirred for 3 hours at room temperature, the mixture was poured into cold water and extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate, and evaporated in vacuo. The oily residue was purified by column chromatography on silica gel (100 g) using chloroform as an eluent to afford 3-[2-(5-bromopentyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]-pyridine (3.48 g).

mp : 111 to 112°C (recrystallized from a mixture of diethyl ether and ethyl acetate)
IR (Nujol) : 1660, 1650 (shoulder), 1625, 1580 cm^{-1}
NMR ($CDCl_3$, δ) : Ca. 1.5-2.1 (6H, m), 3.44 (2H, t, J=6.7Hz), 4.29 (2H, t, J=7.2Hz), 6.77 (1H, d, J=9.6Hz), 6.92 (1H, t, J=6.9Hz), 7.02 (1H, d, J=9.6Hz), 7.33 (1H, t, J=6.8Hz), 7.42-7.64 (5H, m), 7.98 (1H, d, J=7.9Hz), 8.53 (1H, d, J=6.9Hz)

The following compounds (Preparations 10 to 15) were obtained according to a similar manner to that of Preparation 9.

Preparation 10

3-[2-(6-Bromohexyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

mp : 94 to 95°C
IR (Nujol) : 1655, 1630, 1590 cm^{-1}
NMR ($CDCl_3$, δ) : Ca. 1.3-1.7 (4H, m), Ca. 1.7-2.1 (4H, m), 3.42 (2H, t, J=6.7Hz), 4.27 (2H, t, J=7.3Hz), 6.77 (1H, d, J=9.6Hz), 6.93 (1H, t, J=6.9Hz), 7.02 (1H, d, J=9.6Hz), 7.29-7.37 (1H, m), 7.44-7.47 (3H, m), 7.59-7.64 (2H, m), 7.97 (1H, d, J=8.9Hz), 8.55 (1H, d, J=6.9Hz)

Preparation 11

3-[2-(7-Bromoheptyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

IR (Film/NaCl) : 1655, 1630, 1585 cm^{-1}
NMR ($CDCl_3$, δ) : Ca. 1.3-2.2 (10H, m), 3.41 (2H, t, J=6.8Hz), 4.27 (2H, t, J=7.4Hz), 6.76 (1H, d, J=9.6Hz), 6.92 (1H, t, J=6.9Hz), 7.01 (1H, d, J=9.6Hz), 7.32 (1H, t, J=6.8Hz), 7.42-7.64 (5H, m), 7.98 (1H, d, J=7.9Hz), 8.53 (1H, d, J=6.9Hz)

Preparation 12

3-[2-(8-Bromooctyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

mp : 84 to 85°C
IR (Nujol) : 1655, 1630, 1580 cm^{-1}

NMR ($CDCl_3$, δ) : Ca. 1.2-1.7 (8H, broad), Ca. 1.7-2.1 (4H, m), 3.40 (2H, t, J=6.8Hz), 4.27 (2H, t, J=7.4Hz), 6.76 (1H, d, J=9.6Hz), 6.92 (1H, t, J=6.9Hz), 7.01 (1H, d, J=9.6Hz), 7.27-7.35 (1H, m), 7.43-7.47 (3H, m), 7.58-7.64 (2H, m), 7.97 (1H, d, J=8.9Hz), 8.53 (1H, d, J=6.9Hz)

Preparation 13

3-[2-(9-Bromononyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

mp : 85 to 87°C
IR (Nujol) : 1650, 1625, 1580, 1520 cm^{-1}
NMR ($CDCl_3$, δ) : 1.20-1.67 (10H, m), 1.67-2.20 (4H, m), 3.40 (2H, t, J=6.8Hz), 4.27 (2H, t, J=7.4Hz), 6.77 (1H, d, J=9.6Hz), 6.96 (1H, t, J=6.9Hz), 7.00 (1H, d, J=9.6Hz), 7.32 (1H, m), 7.40-7.50 (3H, m), 7.50-7.68 (2H, m), 7.98 (1H, d, J=8.9Hz), 8.55 (1H, d, J=7.0Hz)

Preparation 14

3-[2-(10-Bromodecyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

mp : 59 to 60°C
IR (Nujol) : 1650, 1625, 1585, 1520 cm^{-1}
NMR ($CDCl_3$, δ) : 1.20-1.57 (12H, m), 1.70-2.03 (4H, m), 3.40 (2H, t, J=6.8Hz), 4.27 (2H, t, J=7.4Hz), 6.76 (1H, d, J=9.6Hz), 6.92 (1H, t, J=6.9Hz), 7.00 (1H, d, J=9.6Hz), 7.31 (1H, m), 7.37-7.52 (3H, m), 7.53-7.68 (2H, m), 7.98 (1H, d, J=8.9Hz), 8.54 (1H, d, J=7.0Hz)

Preparation 15

3-[2-(12-Bromododecyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

mp : 70 to 71°C
IR (Nujol) : 1655, 1630, 1590, 1525 cm -1
NMR ($CDCl_3$, δ) : 1.13-1.53 (16H, m), 1.73-2.03 (4H, m), 3.40 (2H, t, J=6.8Hz), 4.27 (2H, t, J=7.4Hz), 6.76 (1H, d, J=9.6Hz), 6.92 (1H, t, J=6.9Hz), 7.00 (1H, d, J=9.6Hz), 7.31 (1H, m), 7.37-7.50 (3H, m), 7.55-7.67 (2H, m), 7.98 (1H, d, J=8.9Hz), 8.53 (1H, d, J=6.0Hz)

Example 26

A mixture of 3-[2-(5-bromopentyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine (2.753 g) and sodium cyanide (0.37 g) in dimethyl sulfoxide (12.6 ml) was stirred at room temperature for 2 hours and then at 60°C for 1 hour. To the mixture was added water and extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel using a mixture of chloroform and methanol as an eluent to afford 3-[2-(5-cyanopentyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]-pyridine (1.75 g).

mp : 120.5 to 122°C (recrystallized from ethyl acetate)
IR (Nujol) : 2245 (weak), 1660, 1630 (shoulder), 1590 cm^{-1}
NMR ($CDCl_3$, δ) : Ca. 1.5-2.1 (6H, m), 2.39 (2H, t, J=6.8Hz), 4.29 (2H, t, J=7.3Hz), 6.77 (1H, d, J=9.6Hz), 6.93 (1H, t, J=6.9Hz), 7.03 (1H, d, J=9.6Hz), 7.34 (1H, t, J=6.8Hz), 7.44-7.64 (5H, m), 7.96 (1H, d, J=7.8Hz), 8.54 (1H, d, J=7Hz)

The following compounds (Examples 27 to 32) were obtained according to a similar manner to that of Example 26.

Example 27

3-[2-(6-Cyanohexyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

mp : 85 to 87°C
IR (Nujol) : 2245 (weak), 1660, 1630, 1590 cm^{-1}
NMR ($CDCl_3$, δ) : Ca. 1.4-1.8 (6H, m), Ca. 1.8-2.1 (2H, m), 2.36 (2H, t, J=6.8Hz), 4.27 (2H, t, J=7.2Hz), 6.77 (1H,

d, J=9.6Hz), 6.93 (1H, t, J=6.9Hz), 7.02 (1H, d, J=9.6Hz), 7.29-7.38 (1H, m), 7.44-7.58 (3H, m), 7.59-7.64 (2H, m), 7.97 (1H, d, J=8.9Hz), 8.54 (1H, d, J=6.9Hz)

Example 28 (Starting Material, not comprised by the claims)

3-[2-(7-Cyanoheptyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

mp : 112 to 113°C (recrystallized from ethyl acetate)
IR (Nujol) : 2250 (weak), 1660, 1630, 1590 cm^{-1}
NMR ($CDCl_3$, δ) : Ca. 1.4-2.1 (10H, m), 2.34 (2H, t, J=6.9Hz), 4.27 (2H, t, J=7.3Hz), 6.76 (1H, d, J=9.6Hz), 6.95 (1H, t, J=6.9Hz), 7.02 (1H, d, J=9.6Hz), 7.33 (1H, t, J=6.8Hz), 7.43-7.64 (5H, m), 7.98 (1H, d, J=8.9Hz), 8.53 (1H, d, J=7Hz)

Example 29 (Starting Material, not comprised by the claims)

3-[2-(8-Cyanooctyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

mp : 94 to 96°C
IR (Nujol) : 2230 (weak), 1650, 1580 cm^{-1}
NMR ($CDCl_3$, δ) : Ca. 1.2-1.8 (10H, broad), Ca. 1.8-2.1 (2H, m), 1.89-1.92 (2H, m), 2.33 (2H, t, J=6.9Hz), 4.27 (2H, t, J=7.4Hz), 6.76 (1H, d, J=9.6Hz), 6.92 (1H, t, J=6.9Hz), 7.01 (1H, d, J=9.6Hz), 7.27-7.36 (1H, m), 7.44-7.58 (3H, m), 7.58-7.64 (2H, m), 7.98 (1H, d, J=8.9Hz), 8.53 (1H, d, J=6.9Hz)

Example 30 (Starting Material, not comprised by the claims)

3-[2-(9-Cyanononyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

mp : 123 to 125°C
IR (Nujol) : 2240, 1655, 1630, 1585, 1525 cm^{-1}
NMR ($CDCl_3$, δ) : 1.20-1.53 (10H, m), 1.53-1.73 (2H, m), 1.80-2.03 (2H, m), 2.33 (2H, t, J=7.0Hz), 4.27 (2H, t, J=7.4Hz), 6.76 (1H, d, J=9.6Hz), 6.92 (1H, t, J=7.2Hz), 7.01 (1H, d, J=9.6Hz), 7.32 (1H, m), 7.40-7.55 (3H, m), 7.55-7.77 (2H, m), 7.98 (1H, d, J=8.9Hz), 8.54 (1H, d, J=6.9Hz)

Example 31 (Starting Material, not comprised by the claims)

3-[2-(10-Cyanodecyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

mp : 77 to 79°C
IR (Nujol) : 2240, 1645, 1580, 1520 cm^{-1}
NMR ($CDCl_3$, δ) : 1.20-1.53 (12H, m), 1.53-1.75 (2H, m), 1.75-2.05 (2H, m), 2.33 (2H, t, J=7.0Hz), 4.27 (2H, t, J=7.4Hz), 6.76 (1H, d, J=9.6Hz), 6.92 (1H, t, J=6.9Hz), 7.00 (1H, d, J=9.6Hz), 7.31 (1H, m), 7.37-7.53 (3H, m), 7.53-7.70 (2H, m), 7.98 (1H, d, J=8.9Hz), 8.53 (1H, d, J=6.9Hz)

Example 32 (Starting Material, not comprised by the claims)

3-[2-(12-Cyanododecyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

mp : 69 to 70°C
IR (Nujol) : 2240, 1655, 1630, 1585, 1530 cm^{-1}
NMR ($CDCl_3$, δ) : 1.20-1.55 (16H, m), 1.55-1.73 (2H, m), 1.83-2.03 (2H, m), 2.33 (2H, t, J=7.0Hz), 4.27 (2H, t, J=7.4Hz), 6.76 (1H, d, J=9.6Hz), 6.91 (1H, t, J=6.9Hz), 7.00 (1H, d, J=9.6Hz), 7.31 (1H, m), 7.37-7.50 (3H, m), 7.53-7.68 (2H, m), 7.98 (1H, d, J=8.9Hz), 8.53 (1H, d, J=6.9Hz)

Example 33

3-[2-Cyanomethyl-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine was obtained according to a similar manner to that of Example 1.

mp : 218-219°C
IR (Nujol) : 1670, 1660 (shoulder), 1625, 1590 cm^{-1}
NMR ($CDCl_3$, δ) : 5.18 (2H, s), 6.78 (1H, d, J=9.8Hz), 6.97 (1H, t, J=6.9Hz), 7.05 (1H, d, J=9.8Hz), 7.39 (1H, t, J=8Hz), 7.46-7.63 (5H, m), 8.15 (1H, d, J=9Hz), 8.55 (1H, d, J=6.9Hz)

The following compounds (Examples 34 to 41) were obtained according to a similar manner to that of Example 21.

Example 34

3-[2-{(1H-Tetrazol-5-yl)methyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

mp : 252 to 254°C (decomp.), (recrystallized from a mixture of chloroform and methanol)
IR (Nujol) : 1650, 1580 cm^{-1}
NMR (DMSO-d_6, δ) : 5.72 (2H, s), 6.97 (1H, d, J=9.7Hz), 7.07 (1H, t, J=6.8Hz), 7.11 (1H, d, J=9.7Hz), 7.40 (1H, t, J=6.8Hz), 7.47-7.66 (5H, m), 7.83 (1H, d, J=8.9Hz), 8.82 (1H, d, J=6.9Hz)

Example 35

3-[2-{5-(1H-Tetrazol-5-yl)pentyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

mp : 167 to 168°C (recrystallized from a mixture of methanol and ethyl acetate)
IR (Nujol) : 1635, 1560 cm^{-1}
NMR (DMSO-d_6, δ) : Ca. 1.3-1.5 (2H, m), Ca. 1.7-1.9 (4H, m), 2.90 (2H, t, J=7.4Hz), 4.14 (2H, t, J=7.1Hz), 6.87 (1H, d, J=9.6Hz), Ca. 7.1 (1H, m), 7.10 (1H, d, J=9.6Hz), Ca. 7.4-7.7 (6H, m), 7.92 (1H, d, J=8.9Hz), 8.83 (1H, d, J=6.9Hz)

Example 36

3-[2-{6-(1H-Tetrazol-5-yl)hexyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

mp : 183 to 185°C (recrystallized from ethanol)
IR (Nujol) : 1640, 1560 cm^{-1}
NMR ($CDCl_3$, δ) : Ca. 1.3-1.7 (4H, broad), Ca. 1.7-2.1 (4H, m), 3.03 (2H, t, J=7.1Hz), 4.31 (2H, t, J=7.0Hz), 6.87 (1H, d, J=9.6Hz), 6.95 (1H, t, J=6.9Hz), 7.12 (1H, d, J=9.6Hz), 7.32-7.39 (1H, m), 7.45-7.48 (3H, m), 7.58-7.63 (2H, m), 7.99 (1H, d, J=8.9Hz), 8.55 (1H, d, J=6.9Hz)

Example 37

3-[2-{7-(1H-Tetrazol-5-yl)heptyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

mp : 189.5 to 190.5°C (recrystallized from a mixture of methanol and ethyl acetate)
IR (Nujol) : 1650, 1580 cm^{-1}
NMR (DMSO-d_6, δ) : Ca. 1.2-1.9 (10H, m), 2.87 (2H, t, J=7.5Hz), 4.13 (2H, t, J=7.1Hz), 6.87 (1H, d, J=9.6Hz), Ca. 7.1 (1H, m), 7.11 (1H, d, J=9.6Hz), Ca. 7.4-7.7 (6H, m), 7.91 (1H, d, J=8.9Hz), 8.82 (1H, d, J=6.9Hz)

Example 38

3-[2-{8-(1H-Tetrazol-5-yl)octyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

mp : 165 to 167°C (recrystallized from ethanol)
IR (Nujol) : 1635, 1550-1565 (broad) cm^{-1}
NMR ($CDCl_3$, δ) : Ca. 1.3-1.6 (8H, broad), Ca. 1.7-2.1 (4H, m), 3.00 (2H, t, J=7.6Hz), 4.34 (2H, t, J=7.2Hz), 6.90 (1H, d, J=9.6Hz), 6.95 (1H, t, J=6.9Hz), 7.11 (1H, d, J=9.6Hz), 7.35 (1H, t, J=7.9Hz), 7.44-7.48 (3H, m), 7.58-7.63 (2H, m), 8.00 (1H, d, J=8.9Hz), 8.55 (1H, d, J=6.9Hz)

Example 39

3-[2-{9-(1H-Tetrazol-5-yl)nonyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

mp : 155 to 156°C
IR (Nujol) : 1635, 1560, 1535, 1490 cm^{-1}
NMR ($CDCl_3$, δ) : 1.13-1.60 (10H, m), 1.65-2.07 (4H, m), 2.99 (2H, t, J=7.8Hz), 4.34 (2H, t, J=7.5Hz), 6.95 (1H, m), 6.96 (1H, d, J=9.6Hz), 7.13 (1H, d, J=9.6Hz), 7.35 (1H, m), 7.43-7.53 (3H, m), 7.53-7.68 (2H, m), 8.00 (1H, d, J=8.9Hz), 8.55 (1H, d, J=7.0Hz), 15.9 (1H, broad s)

Example 40

3-[2-{10-(1H-Tetrazol-5-yl)decyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

mp : 135 to 136°C
IR (Nujol) : 1635, 1560, 1535, 1490 cm^{-1}
NMR ($CDCl_3$, δ) : 1.13-1.57 (12H, m), 1.67-2.07 (4H, m), 2.97 (2H, t, J=7.6Hz), 4.33 (2H, t, J=7.4 Hz), 6.94 (1H, d, J=9.6Hz), 6.98 (1H, m), 7.11 (1H, d, J=9.6Hz), 7.35 (1H, m), 7.40-7.52 (3H, m), 7.52-7.67 (2H, m), 8.00 (1H, d, J=8.9Hz), 8.56 (1H, d, J=7.0Hz)

Example 41

3-[2-{12-(1H-Tetrazol-5-yl)dodecyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

mp : 134 to 135°C
IR (Nujol) : 1635, 1560, 1535, 1490 cm^{-1}
NMR ($CDCl_3$, δ) : 1.10-1.55 (6H, m), 1.73-2.10 (4H, m), 2.96 (2H, t, J=7.5Hz), 4.33 (2H, t, J=7.3Hz), 6.91 (1H, d, J=9.6Hz), 6.96 (1H, m), 7.09 (1H, d, J=9.6Hz), 7.35 (1H, m), 7.40-7.53 (3H, m), 7.53-7.70 (2H, m), 8.00 (1H, d, J=8.9Hz), 8.57 (1H, d, J=7.0Hz)

The following compounds (Examples 42 to 67) were obtained according to a similar manner to that of Example 1.

Example 42

3-[2-(2-Aminoethyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

IR (Nujol) : 3380, 3300, 1660, 1630 cm^{-1}

Example 43

3-[2-{2-(Ethoxycarbonylmethylamino)ethyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

IR (Nujol) : 2750, 2170, 2120, 2430, 1760, 1650, 1630 cm^{-1}

Example 44

3-[2-{2-(Carboxymethylamino)ethyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

IR (Nujol) : 3400, 1650, 1600 cm^{-1}

Example 45

3-[2-{2-{2-Hydroxy-3-(1-naphthyloxy)propylamino}-ethyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo-[1,5-a]pyridine

NMR ($CDCl_3$, δ) : 2.0-3.0 (2H, broad m), 2.9-3.1 (2H, m), 3.1-3.4 (2H, m), 4.0-4.3 (3H, m), 4.3-4.6 (2H, m), 6.7-6.8 (2H, m), 6.8-6.9 (1H, m), 6.98 (1H, d, J=10Hz), 7.0-7.5 (8H, m), 7.5-7.6 (2H, m), 7.7-7.8 (1H, m), 7.9-8.0 (1H, m), 8.1-8.2 (1H, m), 8.4-8.5 (1H, m)

Example 46

3-[2-(4-Dimethylaminobutyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine hydrochloride

IR (Nujol) : 3100, 3050, 2400, 1660, 1630 cm^{-1}

Example 47

3-[2-{2-{4-(2-Hydroxyethyl)piperazin-1-yl}ethyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]-pyridine dihydrochloride

IR (Nujol) : 3400, 1660, 1590 cm^{-1}

Example 48

3-[2-{2-{4-(2-Methoxyphenyl)piperazin-1-yl}ethyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]-pyridine

IR (Nujol) : 1680, 1585, 1525, 1500 cm^{-1}

Example 49

3-[2-{2-(1H-Tetrazol-5-yl)ethyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

IR (Nujol) : 1660, 1585 cm^{-1}

Example 50

3-[2-{3-(1H-Tetrazol-5-yl)propyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

IR (Nujol) : 1665, 1595 cm^{-1}

Example 51

3-[2-{4-(1H-Tetrazol-5-yl)butyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

IR (Nujol) : 1635, 1565 cm^{-1}

Example 52

3-(2-Vinyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-phenylpyrazolo[1,5-a]pyridine

IR (Nujol) : 1680, 1635, 1605 cm^{-1}

Example 53

3-[2-(5-Cyanopentyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

IR (Nujol) : 2245 (weak), 1660, 1630 (shoulder), 1590 cm^{-1}

Example 54

3-[2-(6-Cyanohexyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

IR (Nujol) : 2245 (weak), 1660, 1630, 1590 cm^{-1}

Example 55 Starting Materials, not comprised by the claims

3-[2-(7-Cyanoheptyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

IR (Nujol) : 2250 (weak), 1660, 1630, 1590 cm^{-1}

Example 56 Starting Materials, not comprised by the claims

3-[2-(8-Cyanooctyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

IR (Nujol) : 2230 (weak), 1650, 1580 cm^{-1}

Example 57 Starting Materials, not comprised by the claims

3-[2-(9-Cyanononyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

IR (Nujol) : 2240, 1655, 1630, 1585, 1525 cm^{-1}

Example 58 Starting Materials, not comprised by the claims

3-[2-(10-Cyanodecyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

IR (Nujol) : 2240, 1645, 1580, 1520 cm^{-1}

Example 59 Starting Materials, not comprised by the claims

3-[2-(12-Cyanododecyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

IR (Nujol) : 2240, 1655, 1630, 1585, 1530 cm^{-1}

Example 60

3-[2-{(1H-Tetrazol-5-yl)methyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

IR (Nujol) : 1650, 1580 cm^{-1}

Example 61

3-[2-{5-(1H-Tetrazol-5-yl)pentyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

IR (Nujol) : 1635, 1560 cm^{-1}

Example 62

3-[2-{6-(1H-Tetrazol-5-yl)hexyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

IR (Nujol) : 1640, 1560 cm^{-1}

Example 63

3-[2-{7-(1H-Tetrazol-5-yl)heptyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

IR (Nujol) : 1650, 1580 cm^{-1}

Example 64

3-[2-{8-(1H-Tetrazol-5-yl)octyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

IR (Nujol) : 1635, 1550-1565 (broad) cm^{-1}

Example 65

3-[2-{9-(1H-Tetrazol-5-yl)nonyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

IR (Nujol) : 1635, 1560, 1535, 1490 cm^{-1}

Example 66

3-[2-{10-(1H-Tetrazol-5-yl)decyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

IR (Nujol) : 1635, 1560, 1535, 1490 cm^{-1}

Example 67

3-[2-{12-(1H-Tetrazol-5-yl)dodecyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

IR (Nujol) : 1635, 1560, 1535, 1490 cm^{-1}

The following compounds (Example 68 to 76) were obtained according to a similar manner to that of Example 18.

Example 68

3-[2-(2-Morpholinoethyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine hydrochloride

IR (Nujol) : 2325, 1670, 1590 cm^{-1}

Example 69

3-[2-(2-Piperidinoethyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine hydrochloride

IR (Nujol) : 2495, 1660, 1595 cm^{-1}

Example 70

3-[2-(2-Dimethylaminoethyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine hydrochloride

IR (Nujol) : 3520, 3450, 2600, 2370, 1640, 1570 cm^{-1}

Example 71

3-[2-(3-Dimethylaminopropyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine hydrochloride

IR (Nujol) : 2400, 1655, 1590 cm^{-1}

Example 72

3-[2-(2-Phthalimidoethyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

IR (Nujol) : 1760, 1710, 1660, 1630 cm^{-1}

Example 73

3-[2-(2-Aminoethyl)-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

IR (Nujol) : 3380, 3300, 1660, 1630 cm^{-1}

Example 74

3-[2-{2-(Ethoxycarbonylmethylamino)ethyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

IR (Nujol) : 2750, 2170, 2120, 2430, 1760, 1650, 1630 cm^{-1}

Example 75

3-[2-{2-(Carboxymethylamino)ethyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo[1,5-a]pyridine

IR (Nujol) : 3400, 1650, 1600 cm^{-1}

Example 76

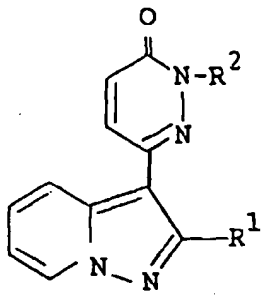
3-[2-{2-{2-Hydroxy-3-(1-naphthyloxy)propylamino}ethyl}-3-oxo-2,3-dihydropyridazin-6-yl]-2-phenylpyrazolo [1,5-a]pyridine

NMR ($CDCl_3$, δ) : 2.0-3.0 (2H, broad m), 2.9-3.1 (2H, m), 3.1-3.4 (2H, m), 4.0-4.3 (3H, m), 4.3-4.6 (2H, m), 6.7-6.8 (2H, m), 6.8-6.9 (1H, m), 6.98 (1H, d, J=10Hz), 7.0-7.5 (8H, m), 7.5-7.6 (2H, m), 7.7-7.8 (1H, m), 7.9-8.0 (1H, m), 8.1-8.2 (1H, m), 8.4-8.5 (1H, m)

Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. A pyrazolopyridine compound of the following formula:



wherein

R^1 is phenyl, and

R^2 is amino(C_1-C_6)alkyl; (C_1-C_6) alkylamino(C_1-C_6)alkyl; carboxy(C_1-C_6)alkylamino(C_1-C_6)alkyl; (C_1-C_6) alkoxycarbonyl(C_1-C_6)alkylamino(C_1-C_6)alkyl; (C_1-C_6)alkylamino(C_1-C_6)alkyl having hydroxy and naphthyloxy; imido(C_1-C_6)alkyl; cyano(C_1-C_6)alkyl; (C_1-C_6) alkyl having heterocyclic group selected from the group consisting of pyridyl, tetrazolyl, piperidyl, piperazinyl, morpholinyl, oxazolidinyl and tetrahydropyranyl, in which heterocyclic group may have 1 to 3 suitable substituent(s) selected from the group consisting of hydroxy(C_1-C_6)alkyl, oxo and phenyl which may have (C_1-C_6)alkoxy; (C_7-C_{20}) alkyl having tetrazolyl; phenyl(C_1-C_6)alkyl; (C_2-C_4)alkenyl; or dihydrochromenyl which may have 1 to 4 suitable substituent(s) selected from the group consisting of (C_1-C_6) alkyl, hydroxy and cyano,

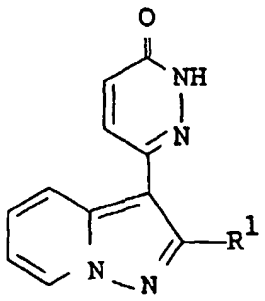
and a pharmaceutically acceptable salt thereof.

2. A compound of claim 1, wherein

R^2 is (C_1-C_6)alkylamino(C_1-C_6)alkyl; (C_1-C_6)alkyl having tetrazolyl, piperidyl or morpholinyl; or (C_7-C_{20})alkyl having tetrazolyl.

3. A process for preparing a pyrazolopyridine compound of claim 1 or a salt thereof, which comprises

i) reacting a compound of the formula :



wherein R^1 is as defined above,
or a salt thereof, with a compound of the formula :

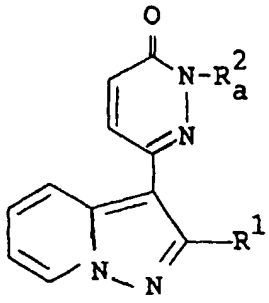
$$R^2 - X$$

wherein

R^2 is as defined above, and
X is a leaving group,

or a salt thereof, or

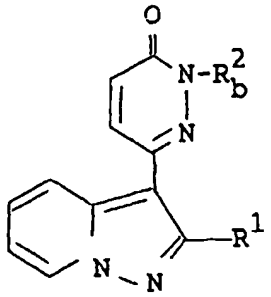
ii) subjecting a compound of the formula :



wherein

R^1 is as defined above, and
R^2_a is imido(C_1-C_6)alkyl

or a salt thereof, to elimination reaction of amino protective group, to give a compound of the formula :

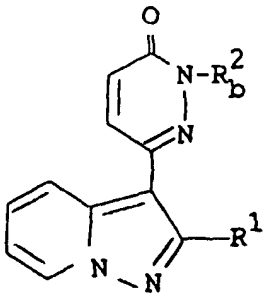


wherein

R^1 is as defined above, and
R_b^2 is amino(C_1-C_6)alkyl,

or a salt thereof, or

iii) reacting a compound of the formula :



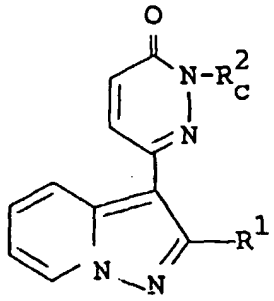
wherein R^1 and R_b^2 are each as defined above, or a salt thereof, with a compound of the formula :

$$R^3 - Y$$

wherein

R^3 is (C_1-C_6)alkyl, carboxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl (C_1-C_6)alkyl or (C_1-C_6) alkyl having hydroxy and naphthyloxy, and
Y is a leaving group,

or a salt thereof, to give a compound of the formula:



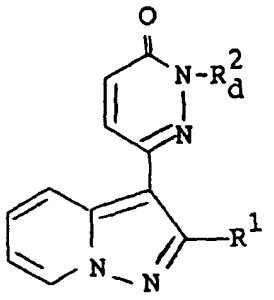
wherein

R^1 is as defined above, and

R^2_c is (C_1-C_6)alkylamino(C_1-C_6)alkyl, carboxy(C_1-C_6)alkylamino(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl (C_1-C_6) alkylamino(C_1-C_6)alkyl or (C_1-C_6)alkylamino(C_1-C_6)alkyl having hydroxy and

naphthyloxy, or a salt thereof, or

iv) subjecting a compound of the formula :

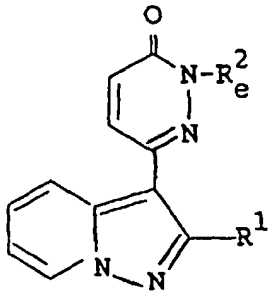


wherein

R^1 is as defined above, and

R^2_d is (C_1-C_6)alkoxycarbonyl (C_1-C_6)alkylamino(C_1-C_6)alkyl,

or a salt thereof, to elimination reaction of carboxy protective group, to give a compound of the formula :



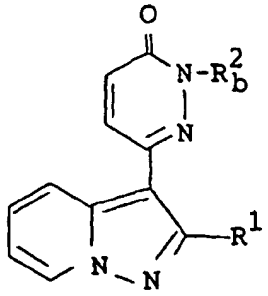
wherein

R^1 is as defined above, and

R^2_e is carboxy(C_1-C_6)alkylamino(C_1-C_6)alkyl,

or a salt thereof, or

v) reacting a compound of the formula :



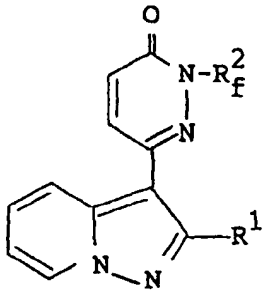
wherein R^1 and R^2_b are each as defined above, or a salt thereof, with a compound of the formula :

$$H - R^4$$

wherein

R^4 is (C_1-C_6)alkyl having epoxy and naphthyloxy,

to give a compound of the formula :

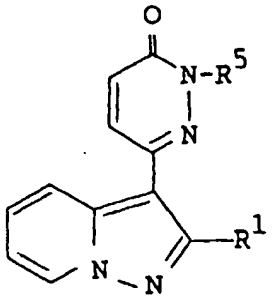


wherein

R^1 is as defined above, and
R^2_f is (C_1-C_6) alkylamino(C_1-C_6)alkyl having hydroxy and naphthyloxy,

or a salt thereof, or

vi) reacting a compound of the formula :



wherein

R^1 is as defined above, and
R^5 is hydroxy(C_1-C_6)alkyl,

or its reactive derivative at hydroxy group
or a salt thereof, with a compound of the formula :

$$H - R^6$$

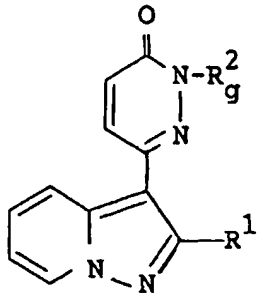
wherein

R^6 is amino; (C_1-C_6)alkylamino; carboxy(C_1-C_6)alkylamino; (C_1-C_6)-alkoxycarbonyl (C_1-C_6)alkylamino; (C_1-C_6)alkylamino having hydroxy and naphthyloxy; a group of the formula :

[in which

is

N-containing heterocyclic group selected from the group consisting of pyridyl, tetrazolyl, piperidyl, piperazinyl, morpholinyl, oxazolidinyl and tetrahydropyranyl, in which heterocyclic group may have 1 to 3 suitable substituent(s) selected from the group consisting of hydroxy(C_1-C_6)alkyl, oxo and phenyl which may have (C_1-C_6) alkoxy]; or imido,
or a salt thereof, to give a compound of the formula:



wherein

R^1 is as defined above, and

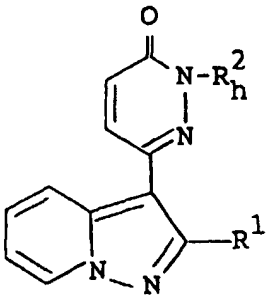
R^2_g is amino(C_1-C_6)alkyl; (C_1-C_6) alkylamino(C_1-C_6)alkyl; carboxy(C_1-C_6)alkylamino(C_1-C_6)alkyl; (C_1-C_6) alkoxycarbonyl(C_1-C_6)-alkylamino(C_1-C_6)alkyl; (C_1-C_6)alkylamino(C_1-C_6)alkyl having hydroxy and naphthyloxy; (C_1-C_6) alkyl having a group of the formula :

[in which

is as defined above]; or imido(C_1-C_6)alkyl,

or a salt thereof, or

vii) subjecting a compound of the formula :

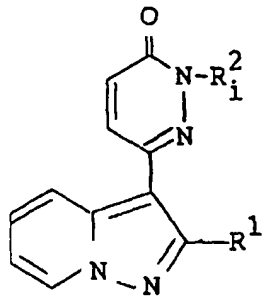


wherein

R^1 is as defined above, and

R^2_h is cyano(C_1-C_6)alkyl or cyano(C_7-C_{20})alkyl,

or a salt thereof, to formation reaction of tetrazolyl group to give a compound of the formula :

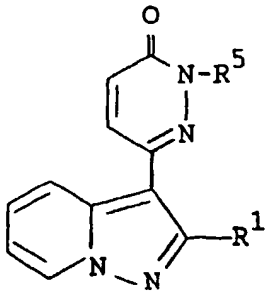


wherein

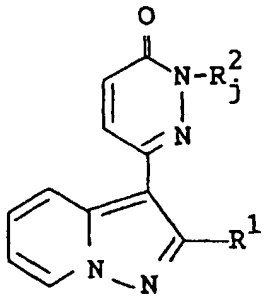
R^1 is as defined above, and
R^2_i is tetrazolyl(C_1-C_6)alkyl or tetrazolyl(C_7-C_{20})alkyl,

or a salt thereof, or

viii) subjecting a compound of the formula :



wherein R^1 and R^5 are each as defined above, or a salt thereof, to dehydration reaction, to give a compound of the formula :

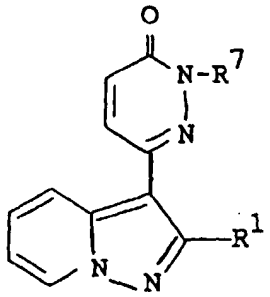


wherein

R^1 is as defined above, and
R^2_j is (C_2-C_4) alkenyl,

or a salt thereof, or

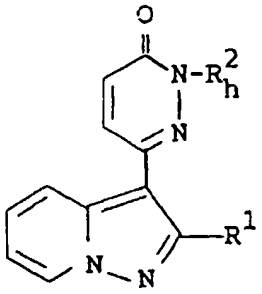
ix) subjecting a compound of the formula :



wherein

R^1 is as defined above, and
R^7 is halo(C_1-C_6)alkyl,

or a salt thereof, to cyanation reaction, to give a compound of the formula :



wherein

R^1 is as defined above, and
R^2_h is cyano(C_1-C_6)alkyl,

or a salt thereof.

4. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier or excipient.

5. A compound of claim 1 and a pharmaceutically acceptable salt thereof for use as a medicament.

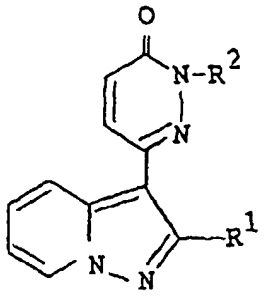
6. Use of a compound of claim 1 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament.

7. A compound of claim 1 and a pharmaceutically acceptable salt thereof for use in treating and/or preventing melancholia, heart failure, hypertension, renal failure, renal toxicity, nephrosis, nephritis, edema, obesity, bronchial asthma, gout, hyperuricemia, sudden infant death syndrome, immunosuppresion, diabetes, ulcer, pancreatitis, myocardiac infarction, thrombosis, obstruction, arteriosclerosis obliterans, thrombophlebitis, cerebral infarction, transient ischemic attack or angina pectoris.

8. A pharmaceutical composition of claim 4, which is an adenosine antagonist.

Claims for the following Contracting States : ES, GR

1. A process for preparing pyrazolopyridine compound of the following formula:



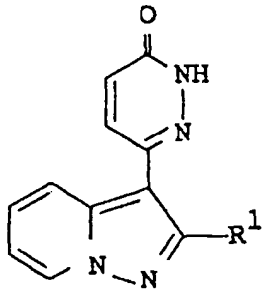
wherein

R^1 is phenyl, and

R^2 is amino(C_1-C_6)alkyl; (C_1-C_6) alkylamino(C_1-C_6)alkyl; carboxy(C_1-C_6)alkylamino(C_1-C_6)alkyl; (C_1-C_6) alkoxycarbonyl(C_1-C_6)alkylamino(C_1-C_6)alkyl; (C_1-C_6)alkylamino(C_1-C_6)alkyl having hydroxy and naphthyloxy; imido(C_1-C_6)alkyl; cyano(C_1-C_6)alkyl; (C_1-C_6) alkyl having heterocyclic group selected from the group consisting of pyridyl, tetrazolyl, piperidyl, piperazinyl, morpholinyl, oxazolidinyl and tetrahydropyranyl, in which heterocyclic group may have 1 to 3 suitable substituent(s) selected from the group consisting of hydroxy(C_1-C_6)alkyl, oxo and phenyl which may have (C_1-C_6)alkoxy; (C_7-C_{20}) alkyl having tetrazolyl; phenyl(C_1-C_6)alkyl; (C_2-C_4)alkenyl; or dihydrochromenyl which may have 1 to 4 suitable substituent(s) selected from the group consisting of (C_1-C_6) alkyl, hydroxy and cyano,

and a pharmaceutically acceptable salt thereof,
which comprises

i) reacting a compound of the formula :



wherein

R^1 is as defined above,

or a salt thereof, with a compound of the formula :

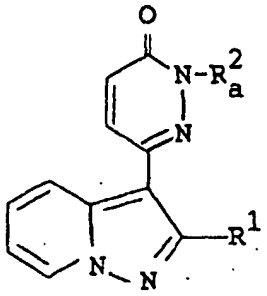
$$R^2 - X$$

wherein

R^2 is as defined above, and
X is a leaving group,

or a salt thereof, or

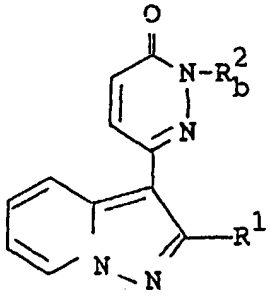
ii) subjecting a compound of the formula :



wherein

R^1 is as defined above, and
R^2_a is imido (C_1-C_6)alkyl

or a salt thereof, to elimination reaction of amino protective group, to give a compound of the formula :

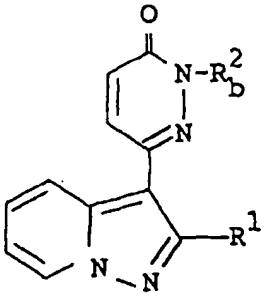


wherein

R^1 is as defined above, and
R^2_b is amino(C_1-C_6)alkyl,

or a salt thereof, or

iii) reacting a compound of the formula :



wherein

R^1 and R^2_b are each as defined above,

or a salt thereof, with a compound of the formula :

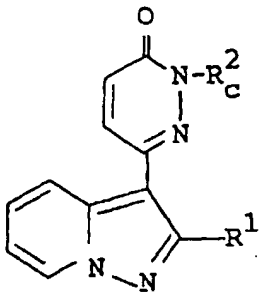
$$R^3 - Y$$

wherein

R^3 is (C_1-C_6)alkyl, carboxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl (C_1-C_6)alkyl or (C_1-C_6) alkyl having hydroxy and naphthyloxy and

Y is a leaving group,

or a salt thereof, to give a compound of the formula:



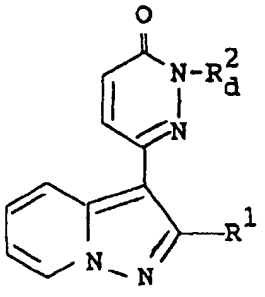
wherein

R^1 is as defined above, and

R^2_c is (C_1-C_6)alkylamino(C_1-C_6)alkyl, carboxy(C_1-C_6)alkylamino(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl (C_1-C_6) alkylamino(C_1-C_6)alkyl or (C_1-C_6)alkylamino(C_1-C_6)alkyl having hydroxy and naphthyloxy,

or a salt thereof, or

iv) subjecting a compound of the formula :

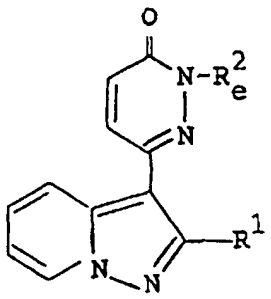


wherein

R^1 is as defined above, and

R^2_d is (C_1-C_6)alkoxycarbonyl(C_1-C_6)alkylamino(C_1-C_6)alkyl,

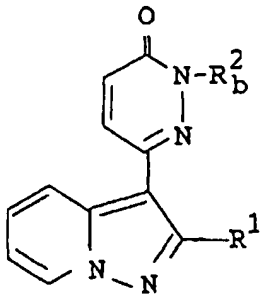
or a salt thereof, to elimination reaction of carboxy protective group, to give a compound of the formula :



wherein

R^1 is as defined above, and
R^2_e is carboxy(C_1-C_6)alkylamino(C_1-C_6)alkyl, or a salt thereof, or

v) reacting a compound of the formula :



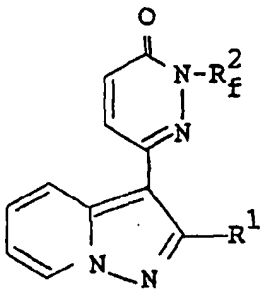
wherein R^1 and R^2_b are each as defined above, or a salt thereof, with a compound of the formula :

$$H - R^4$$

wherein

R^4 is (C_1-C_6)alkyl having epoxy and naphthyloxy,

to give a compound of the formula :



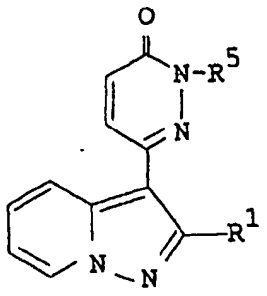
wherein

R^1 is as defined above, and

R^2_f is (C_1-C_6)alkylamino(C_1-C_6)alkyl having hydroxy and naphthyloxy

or a salt thereof, or

vi) reacting a compound of the formula :



wherein

R^1 is as defined above, and
R^5 is hydroxy(C_1-C_6)alkyl,

or its reactive derivative at hydroxy group
or a salt thereof, with a compound of the formula :

$$H - R^6$$

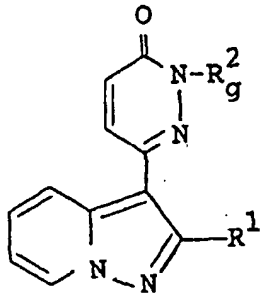
wherein

R^6 is amino; (C_1-C_6)alkylamino; carboxy(C_1-C_6)alkylamino; (C_1-C_6)-alkoxycarbonyl (C_1-C_6)alkylamino; (C_1-C_6)alkylamino having hydroxy and naphthyloxy; a group of the formula :

[in which

is

N-containing heterocyclic group selected from the group consisting of pyridyl, tetrazolyl, piperidyl, piperazinyl morpholinyl, oxazolidinyl and tetrahydropyranyl, in which heterocyclic group may have 1 to 3 suitable substituent(s) selected from the group consisting of hydroxy(C_1-C_6)alkyl oxo and phenyl which may have (C_1-C_6) alkoxy]; or imido,
or a salt thereof, to give a compound of the formula:



wherein

R^1 is as defined above, and

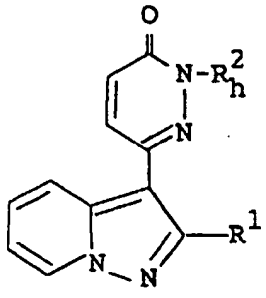
R^2_g is amino(C_1-C_6)alkyl; (C_1-C_6)alkylamino(C_1-C_6)alkyl; carboxy(C_1-C_6)alkylamino(C_1-C_6)alkyl; (C_1-C_6) alkoxycarbonyl(C_1-C_6)alkylamino(C_1-C_6)alkyl; (C_1-C_6)alkylamino(C_1-C_6)alkyl having hydroxy and naphthyloxy; (C_1-C_6) alkyl having a group of the formula :

[in which

is as defined above]; or imido(C_1-C_6)alkyl,

or a salt thereof, or

vii) subjecting a compound of the formula :

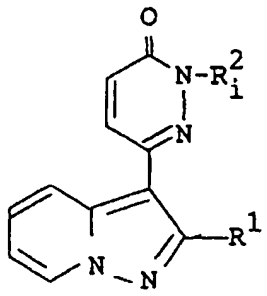


wherein

R^1 is as defined above, and

R^2_h is cyano(C_1-C_6)alkyl or cyano(C_7-C_{20})alkyl,

or a salt thereof, to formation reaction of tetrazolyl group to give a compound of the formula :

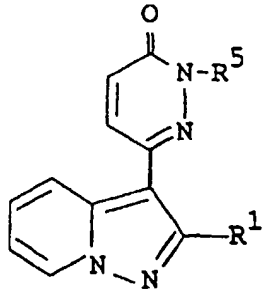


wherein

R^1 is as defined above, and
R^2_i is tetrazolyl(C_1-C_6)alkyl or tetrazolyl(C_7-C_{20})alkyl,

or a salt thereof, or

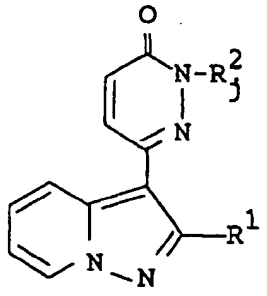
viii) subjecting a compound of the formula :



wherein

R^1 and R^5 are each as defined above,

or a salt thereof, to dehydration reaction, to give a compound of the formula :

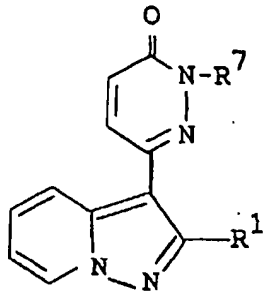


wherein

R^1 is as defined above, and
R^2_j is (C_2-C_4) alkenyl,

or a salt thereof, or

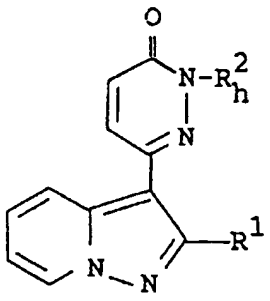
ix) subjecting a compound of the formula :



wherein

R^1 is as defined above, and
R^7 is halo(C_1-C_6)alkyl,

or a salt thereof, to cyanation reaction, to give a compound of the formula :



wherein

R^1 is as defined above, and
R^2_h is cyano(C_1-C_6)alkyl,

or a salt thereof.

2. The process of claim 1, wherein

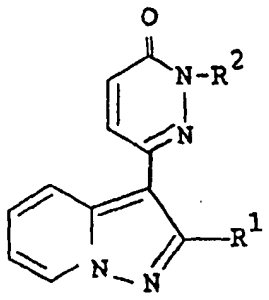
R^2 is (C_1-C_6)alkylamino(C_1-C_6)alkyl; (C_1-C_6)alkyl having tetrazolyl, piperidyl or morpholinyl; or (C_7-C_{20})alkyl having tetrazolyl.

3. Modification of the processes according to claims 1 or 2 which comprises compounding the pyrazolopyridine compound obtained with a usual non-toxic, pharmaceutical acceptable carrier.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Pyrazolopyridinverbindung der folgenden Formel:



worin

R^1 Phenyl ist und

R^2 Amino(C_1-C_6)alkyl; (C_1-C_6)Alkylamino(C_1-C_6)alkyl; Carboxy(C_1-C_6)alkylamino(C_1-C_6)alkyl; (C_1-C_6)Alkoxycarbonyl(C_1-C_6)alkylamino(C_1-C_6)alkyl; (C_1-C_6)Alkylamino(C_1-C_6)alkyl mit Hydroxy und Naphthyloxy; Imido(C_1-C_6)alkyl; Cyano(C_1-C_6)alkyl; (C_1-C_6)Alkyl mit einer heterocyclischen Gruppe, die ausgewählt wird aus der Gruppe, die besteht aus Pyridyl, Tetrazolyl, Piperidyl, Piperazinyl, Morpholinyl, Oxazolidinyl und Tetrahydropyranyl, worin die heterocyclische Gruppe 1 bis 3 geeignete Substituent(en) aufweisen kann, die aus der Gruppe ausgewählt sind, die besteht aus Hydroxy(C_1-C_6)alkyl, Oxo und Phenyl, welches (C_1-C_6)Alkoxy aufweisen kann; (C_7-C_{20})Alkyl mit Tetrazolyl; Phenyl(C_1-C_6)alkyl; (C_2-C_4)Alkenyl; oder Dihydrochromenyl ist, das 1 bis 4 geeignete Substituent(en) aufweisen kann, die aus der Gruppe ausgewählt werden, die aus (C_1-C_6)Alkyl, Hydroxy und Cyano besteht,

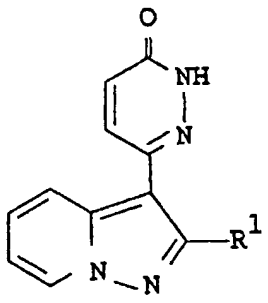
und pharmazeutisch verträgliche Salze davon.

2. Verbindung nach Anspruch 1, worin

R^2 (C_1-C_6)Alkylamino(C_1-C_6)alkyl; (C_1-C_6)Alkyl mit Tetrazolyl, Piperidyl oder Morpholinyl; oder (C_7-C_{20})Alkyl mit Tetrazolyl ist.

3. Verfahren zur Herstellung einer Pyrazolopyridinverbindung nach Anspruch 1 oder eines Salzes davon, das umfaßt:

i) Umsetzen einer Verbindung der Formel:



worin

R^1 wie oben definiert ist,

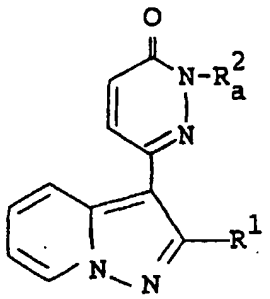
oder eines Salzes davon mit einer Verbindung der Formel:

$$R^2 - X$$

worin

R^2 wie oben definiert ist, und
X eine Abgangsgruppe ist oder einem Salz oder

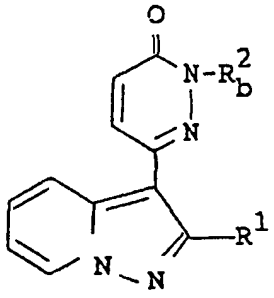
ii) Unterwerfen einer Verbindung der Formel:



worin

R^1 wie oben definiert ist und
R^2_a Imido(C_1-C_6)alkyl ist,

oder eines Salzes davon, der Eliminierungsreaktion der Aminoschutzgruppe, um eine Verbindung der Formel:

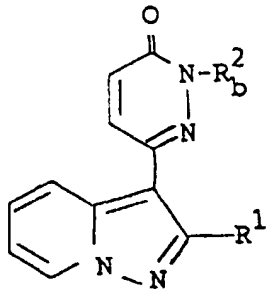


worin

R^1 wie oben definiert ist, und
R^2_b Amino(C_1-C_6)alkyl ist,

oder ein Salz davon zu erhalten, oder

iii) Umsetzen einer Verbindung der Formel:



worin

R^1 und R^2_b jeweils wie oben definiert sind,

oder eines Salzes davon mit einer Verbindung der Formel:

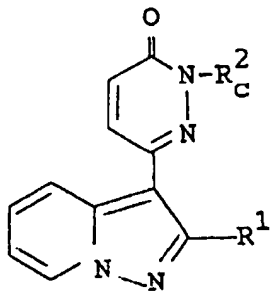
$$R^3 - Y$$

worin

R^3 $(C_1\text{-}C_6)$Alkyl, Carboxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$-Alkoxycarbonyl$(C_1\text{-}C_6)$alkyl oder $(C_1\text{-}C_6)$-Alkyl mit Hydroxy und Naphthyloxy ist, und

Y eine Abgangsgruppe ist,

oder einem Salz davon, um eine Verbindung der Formel:



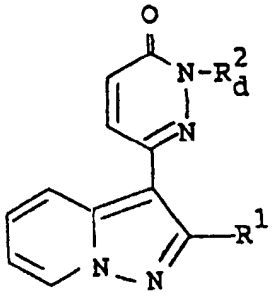
worin

R^1 wie oben definiert ist und

R^2_c $(C_1\text{-}C_6)$Alkylamino$(C_1\text{-}C_6)$alkyl, Carboxy$(C_1\text{-}C_6)$alkylamino$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$Alkoxycarbonyl$(C_1\text{-}C_6)$ alkylamino$(C_1\text{-}C_6)$alkyl oder $(C_1\text{-}C_6)$Alkylamino$(C_1\text{-}C_6)$alkyl mit Hydroxy und Naphthyloxy ist,

oder ein Salz davon zu ergeben, oder

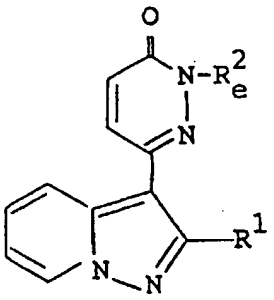
iv) Unterwerfen einer Verbindung der Formel:



worin

R^1 wie oben definiert ist und
R^2_b (C_1-C_6)Alkoxycarbonyl(C_1-C_6)alkylamino(C_1-C_6)alkyl ist,

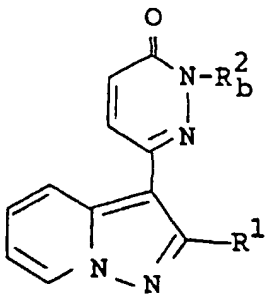
oder eines Salzes davon, der Eliminerungsreaktion der Carboxyschutzgruppe, um eine Verbindung der Formel:



worin

R^1 wie oben definiert ist, und
R^2_e Carboxy(C_1-C_6)alkylamino(C_1-C_6)alkyl ist oder ein Salz davon zu ergeben, oder

v) Umsetzen einer Verbindung der Formel:



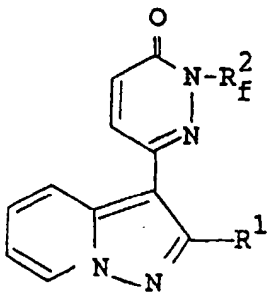
worin

R^1 und R^2_b jeweils wie oben definiert sind,

oder eines Salzes davon mit einer Verbindung der Formel:

$$H - R^4$$

worin R^4 (C_1-C_6)Alkyl mit Epoxy und Naphthyloxy ist, um eine Verbindung der Formel:

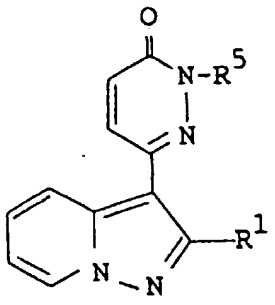


worin

R^1 wie oben definiert ist und
R^2_f (C_1-C_6)Alkylamino(C_1-C_6)alkyl mit Hydroxy und Naphthyloxy ist

oder ein Salz davon zu ergeben, oder

vi) Umsetzen einer Verbindung der Formel:



worin

R^1 wie oben definiert ist und
R^5 Hydroxy(C_1-C_6)alkyl ist,

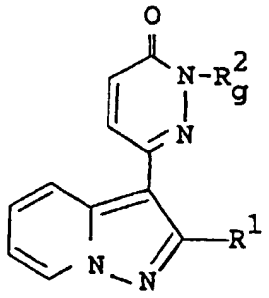
oder eines reaktiven Derivates an der Hydroxygruppe oder eines Salzes davon mit einer Verbindung der Formel:

$$H - R^6$$

worin R^6 Amino; (C_1-C_6)Alkylamino; Carboxy(C_1-C_6)alkylamino; (C_1-C_6)Alkoxycarbonyl(C_1-C_6)alkylamino; (C_1-C_6)Alkylamino mit Hydroxy und Naphthyloxy; eine Gruppe der Formel:

[worin

eine N-enthaltende heterocyclische Gruppe ist, die aus der Gruppe ausgewählt wird, die besteht aus Pyridyl, Tetrazolyl, Piperidyl, Piperazinyl, Morpholinyl, Oxazolidinyl und Tetrahydropyranyl, wobei die heterocyclische Gruppe 1 bis 3 geeignete Substituent(en) aufweisen kann, die aus der Gruppe ausgewählt werden, die aus Hydroxy(C_1-C_6)alkyl, Oxo und Phenyl, das (C_1-C_6)Alkoxy aufweisen kann]; oder Imido ist,
oder einem Salz davon, um eine Verbindung der Formel:



worin

R^1 wie oben definiert ist und

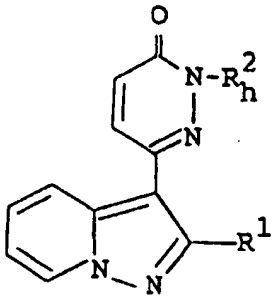
R^2_g Amino(C_1-C_6)alkyl; (C_1-C_6)Alkylamino(C_1-C_6) alkyl; Carboxy(C_1-C_6)alkylamino(C_1-C_6)alkyl; Alkylamino(C_1-C_6)alkyl; (C_1-C_6)Alkylamino(C_1-C_6)alkyl mit Hydroxy und Naphthyloxy; (C_1-C_6)Alkyl mit einer Gruppe der Formel:

[worin

wie oben definiert ist; oder Imido(C_1-C_6)alkyl ist,

oder ein Salz davon zu ergeben, oder

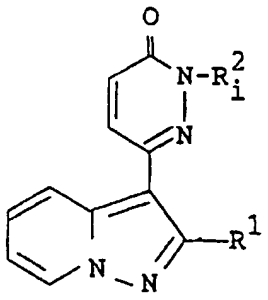
vii) Unterwerfen einer Verbindung der Formel:



worin

R^1 wie oben definiert ist und

R^2_h Cyano(C_1-C_6)alkyl oder Cyano(C_7-C_{20})alkyl ist, oder eines Salzes davon der Bildungsreaktion der Tetrazolylgruppe, um eine Verbindung der Formel:



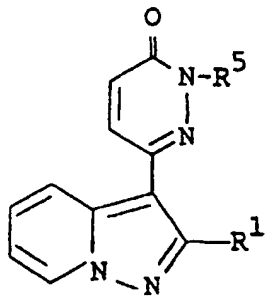
worin

R^1 wie oben definiert ist, und

R^2_i Tetrazolyl(C_1-C_6)alkyl oder Tetrazoyl(C_7-C_{20})alkyl ist

oder ein Salz davon zu ergeben, oder

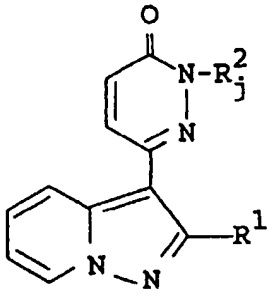
viii) Unterwerfen einer Verbindung der Formel:



worin

R^1 und R^5 jeweils wie oben definiert sind,

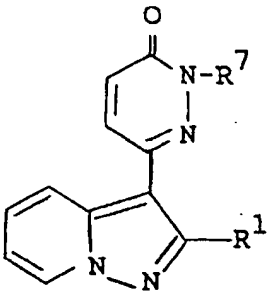
oder eines Salzes davon, der Dehydratisierungsreaktion, um eine Verbindung der Formel:



worin

R^1 wie oben definiert ist, und
R^2_j (C_2-C_4)Alkenyl ist oder ein Salz davon zu ergeben oder

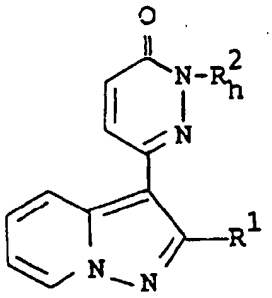
ix) Unterwerfen einer Verbindung der Formel:



worin

R^1 wie oben definiert ist und
R^7 Halogen(C_1-C_6)alkyl ist,

oder eines Salzes davon der Cyanierungsreaktion, um eine Verbindung der Formel:



worin

R^1 wie oben definiert ist und

R^2_a Cyano(C_1-C_6)alkyl ist

oder ein Salz davon zu ergeben.

4. Pharmazeutische Zusammensetzung, die als aktiven Bestandteil eine Verbindung nach Anspruch 1 oder ein pharmazeutisch verträgliches Salz davon in Zusammenmischung mit pharmazeutisch verträglichen Trägern oder Exzipienten umfaßt.

5. Verbindung nach Anspruch 1 und pharmazeutisch verträgliche Salze davon zur Verwendung als Medikament.

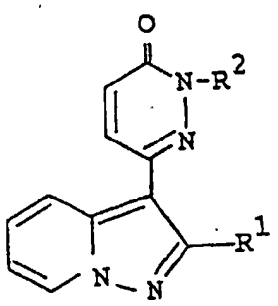
6. Verwendung einer Verbindung nach Anspruch 1 oder eines pharmazeutisch verträglichen Salzes davon für die Herstellung eines Medikaments.

7. Verbindung nach Anspruch 1 und ein pharmazeutisch verträgliches Salz davon zur Verwendung in der Behandlung und/oder Prävention von endogener Depression, Herzversagen, Bluthochdruck, Nierenversagen, Nierenvergiftung, Nephrose, Nephritis, Ödemen, Fettleibigkeit, Bronchialasthma, Gicht, Hyperurikämie, plötzlichem Kindstod (SIDS), Immunsuppression, Diabetes, Geschwüren, Pankreatitis, Myokardinfarkt, Thrombosen, Arteriosclerosis obliterans, Thrombophlebitis, Hirninfarkt, vorübergehender ischämischer Anfall oder Angina pectoris.

8. Pharmazeutische Zusammensetzung nach Anspruch 4, bei der es sich um einen Adenosin-Antagonisten handelt.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung einer Pyrazolopyridinverbindung der folgenden Formel:



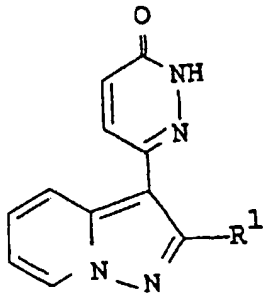
worin

R^1 Phenyl ist und

R^2 Amino(C_1-C_6)alkyl; (C_1-C_6)Alkylamino(C_1-C_6)alkyl; Carboxy(C_1-C_6)alkylamino(C_1-C_6)alkyl; (C_1-C_6)Alkoxycarbonyl(C_1-C_6)alkylamino(C_1-C_6)alkyl; (C_1-C_6)Alkylamino(C_1-C_6)alkyl mit Hydroxy und Naphthyloxy; Imido (C_1-C_6)alkyl; Cyano(C_1-C_6)alkyl; (C_1-C_6)Alkyl mit einer heterocyclischen Gruppe, die ausgewählt wird aus der Gruppe, die besteht aus Pyridyl, Tetrazolyl, Piperidyl, Piperazinyl, Morpholinyl, Oxazolidinyl und Tetrahydropyranyl, worin die heterocyclische Gruppe 1 bis 3 geeignete Substituent(en) aufweisen kann, die aus der Gruppe ausgewählt sind, die besteht aus Hydroxy(C_1-C_6)alkyl, Oxo und Phenyl, welches (C_1-C_6)Alkoxy aufweisen kann; (C_7-C_{20})Alkyl mit Tetrazolyl; Phenyl(C_1-C_6)alkyl; (C_2-C_4)Alkenyl; oder Dihydrochromenyl ist, das 1 bis 4 geeignete Substituent(en) aufweisen kann, die aus der Gruppe ausgewählt werden, die aus (C_1-C_6)Alkyl, Hydroxy und Cyano besteht,

und eines pharmazeutisch verträglichen Salzes davon, das umfaßt:

i) Umsetzen einer Verbindung der Formel:



worin

R^1 wie oben definiert ist,

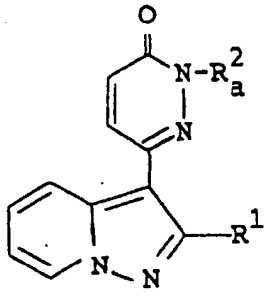
oder eines Salzes davon mit einer Verbindung der Formel:

$$R^2 - X$$

worin

R^2 wie oben definiert ist, und
X eine Abgangsgruppe ist oder einem Salz oder

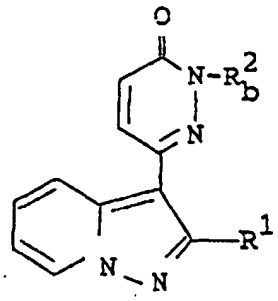
ii) Unterwerfen einer Verbindung der Formel:



worin

R^1 wie oben definiert ist und
R^2_a Imido(C_1-C_6)alkyl ist,

oder eines Salzes davon, der Eliminierungsreaktion der Aminoschutzgruppe, um eine Verbindung der Formel:

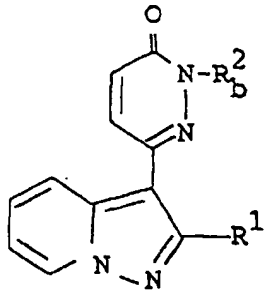


worin

R^1 wie oben definiert ist, und
R^2_b Amino(C_1-C_6)alkyl ist,

oder ein Salz davon zu erhalten, oder

iii) Umsetzen einer Verbindung der Formel:



worin

R^1 und R^2_b jeweils wie oben definiert sind,

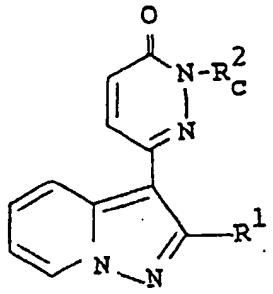
oder eines Salzes davon mit einer Verbindung der Formel:

$$R^3 - Y$$

worin

R^3 (C_1-C_6)Alkyl, Carboxy(C_1-C_6)alkyl, (C_1-C_6)-Alkoxycarbonyl(C_1-C_6)alkyl oder (C_1-C_6)Alkyl mit Hydroxy und Naphthyloxy ist, und
Y eine Abgangsgruppe ist,

oder einem Salz davon, um eine Verbindung der Formel:



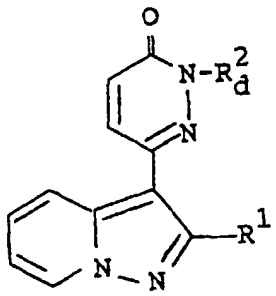
worin

R^1 wie oben definiert ist und

R^2_c (C_1-C_6)Alkylamino(C_1-C_6)alkyl, Carboxy(C_1-C_6)alkylamino(C_1-C_6)alkyl, (C_1-C_6)Alkoxycarbonyl(C_1-C_6)alkylamino(C_1-C_6)alkyl oder (C_1-C_6)Alkylamino(C_1-C_6)alkyl mit Hydroxy und Naphthyloxy ist,

oder ein Salz davon zu ergeben, oder

iv) Unterwerfen einer Verbindung der Formel:

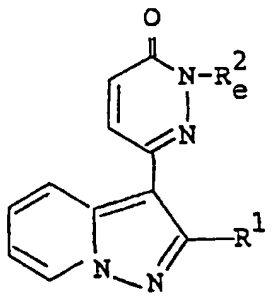


worin

R^1 wie oben definiert ist und

R^2_b (C_1-C_6)Alkoxcarbonyl(C_1-C_6)alkylamino(C_1-C_6)alkyl ist,

oder eines Salzes davon, der Eliminerungsreaktion der Carboxyschutzgruppe, um eine Verbindung der Formel:

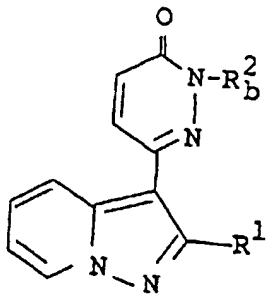


worin

R^1 wie oben definiert ist, und
R^2_e Carboxy(C_1-C_6)alkylamino(C_1-C_6)alkyl ist

oder ein Salz davon zu ergeben, oder

v) Umsetzen einer Verbindung der Formel:



worin

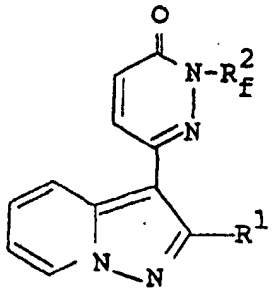
R^1 und R^2_b jeweils wie oben definiert sind,

oder eines Salzes davon mit einer Verbindung der Formel:

$$H - R^4$$

worin

R^4 (C_1-C_6)Alkyl mit Epoxy und Naphthyloxy ist, um eine Verbindung der Formel:

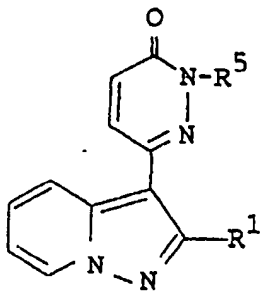


worin

R^1 wie oben definiert ist und
R^2_f (C_1-C_6)Alkylamino(C_1-C_6)alkyl mit Hydroxy und Naphthyloxy ist

oder ein Salz davon zu ergeben, oder

vi) Umsetzen einer Verbindung der Formel:



worin

R^1 wie oben definiert ist und
R^5 Hydroxy(C_1-C_6)alkyl ist,

oder eines reaktiven Derivates an der Hydroxygruppe oder eines Salzes davon mit einer Verbindung der Formel:

$$H - R^6$$

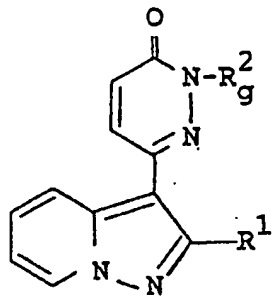
worin

R^6 Amino; (C_1-C_6)Alkylamino; Carboxy(C_1-C_6)alkylamino; (C_1-C_6)Alkoxycarbonyl(C_1-C_6)alkylamino; (C_1-C_6)Alkylamino mit Hydroxy und Naphthyloxy; eine Gruppe der Formel:

[worin

eine N-enthaltende heterocyclische Gruppe ist, die aus der Gruppe ausgewählt wird, die besteht aus Pyridyl, Tetrazolyl, Piperidyl, Piperazinyl, Morpholinyl, Oxazolidinyl und Tetrahydropyranyl, wobei die heterocyclische Gruppe 1 bis 3 geeignete Substituent(en) aufweisen kann, die aus der Gruppe ausgewählt werden, die aus Hydroxy(C_1-C_6)alkyl, Oxo und Phenyl, das (C_1-C_6)Alkoxy aufweisen kann]; oder Imido ist,

oder einem Salz davon, um eine Verbindung der Formel:



worin

R^1 wie oben definiert ist und

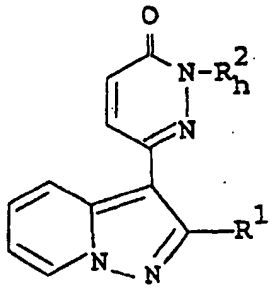
R^2_g Amino(C_1-C_6)alkyl; (C_1-C_6)Alkylamino(C_1-C_6) alkyl; Carboxy(C_1-C_6)alkylamino(C_1-C_6)alkyl; Alkylamino(C_1-C_6)alkyl; (C_1-C_6)Alkylamino(C_1-C_6)alkyl mit Hydroxy und Naphthyloxy; (C_1-C_6)Alkyl mit einer Gruppe der Formel:

[worin

wie oben definiert ist; oder Imido(C_1-C_6)alkyl ist,

oder ein Salz davon zu ergeben, oder

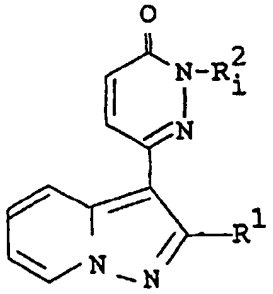
vii) Unterwerfen einer Verbindung der Formel:



worin

R^1 wie oben definiert ist und

R^2_h Cyano(C_1-C_6)alkyl oder Cyano(C_7-C_{20})alkyl ist, oder eines Salzes davon der Bildungsreaktion der Tetrazolylgruppe, um eine Verbindung der Formel:



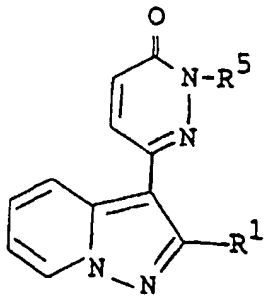
worin

R^1 wie oben definiert ist, und

R^2_i Tetrazolyl(C_1-C_6)alkyl oder Tetrazoyl(C_7-C_{20})alkyl ist

oder ein Salz davon zu ergeben, oder

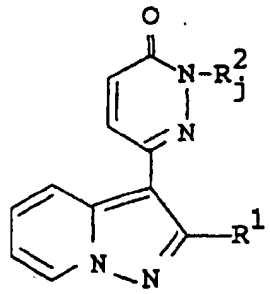
viii) Unterwerfen einer Verbindung der Formel:



worin

R^1 und R^5 jeweils wie oben definiert sind,

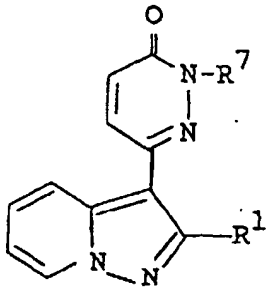
oder eines Salzes davon, der Dehydratisierungsreaktion, um eine Verbindung der Formel:



worin

R^1 wie oben definiert ist, und
R^2_j (C_2-C_4)Alkenyl ist oder ein Salz davon zu ergeben oder

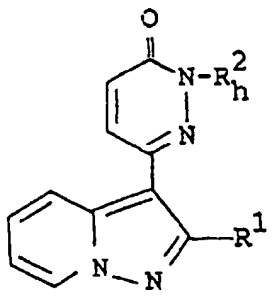
ix) Unterwerfen einer Verbindung der Formel:



worin

R^1 wie oben definiert ist und
R^7 Halogen(C_1-C_6)alkyl ist,

oder eines Salzes davon der Cyanierungsreaktion, um eine Verbindung der Formel:



worin

R^1 wie oben definiert ist und
R^2_a Cyano(C_1-C_6)alkyl ist

oder ein Salz davon zu ergeben.

2. Verfahren nach Anspruch 1, worin

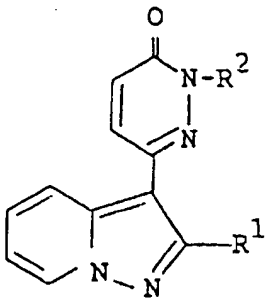
R^2 (C_1-C_6)Alkylamino(C_1-C_6)alkyl; (C_1-C_6)Alkyl mit Tetrazolyl, Piperidyl oder Morpholinyl; oder (C_7-C_{20})Alkyl mit Tetrazolyl ist.

3. Modifizierung der Verfahren nach Anspruch 1 oder 2, die das Mischen der erhaltenen Pyrarolopyridinverbindung mit einem üblichen nichtgiftigen, pharmazeutische verträglichen Träger umfaßt.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Composé de pyrazolopyridine ayant la formule suivante:



dans laquelle

R^1 est un phényle, et
R^2 est un aminoalkyle en C_1-C_6;
un alkyl(en C_1-C_6)aminoalkyle en C_1-C_6;
un carboxyalkyl(en C_1-C_6)aminoalkyle en C_1-C_6; un alcoxy(en C_1-C_6)carbonylalkyl(en C_1-C_6)aminoalkyle en C_1-C_6; un alkyl(en C_1-C_6)aminoalkyle en C_1-C_6 ayant un hydroxy et un naphtyloxy; un imidoalkyle en C_1-C_6; un cyanoalkyle en C_1-C_6; un alkyle en C_1-C_6 ayant un groupe hétérocyclique choisi dans le groupe constitué par un pyridyle, un tétrazolyle, un pipéridyle, un pipérazinyle, un morpholinyle, un oxazolidinyle et un tétrahydropyranyle, dans lequel le groupe hétérocyclique peut avoir 1 à 3 substituants appropriés choisis dans le groupe constitué par un hydroxyalkyle en C_1-C_6, un oxo et un phényle qui

peut avoir un alcoxy en C_1-C_6; un alkyle en C_7-C_{20} ayant un tétrazolyle; un phénylalkyle en C_1-C_6; un alcényle en C_2-C_4; ou un dihydrochrométnyle qui peut avoir 1 à 4 substituants appropriés choisis dans le groupe constitué par un alkyle en C_1-C_6, un hydroxy et un cyano,

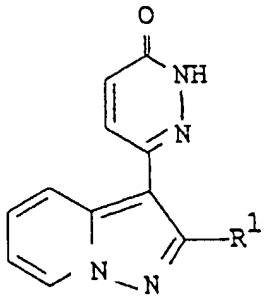
et un sel pharmaceutiquement acceptable de celui-ci.

2. Composé de la revendication 1, dans lequel

R^2 est un alkyl(en C_1-C_6)aminoalkyle en C_1-C_6; un alkyle en C_1-C_6 ayant un tétrazolyle, un pipéridyle ou un morpholinyle; ou un alkyle en C_7-C_{20} ayant un tétrazolyle.

3. Procédé pour la préparation d'un composé de pyrazolopyridine de la revendication 1, ou d'un sel de celui-ci, qui comprend

i) le fait de faire réagir un composé de formule:



dans laquelle R^1 est tel que défini ci-dessus,
ou un sel de celui-ci, avec un composé de formule:

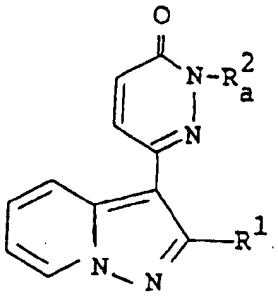
$$R^2 - X$$

dans laquelle

R^2 est tel que défini ci-dessus, et
X est un groupe partant,

ou un sel de celui-ci, ou

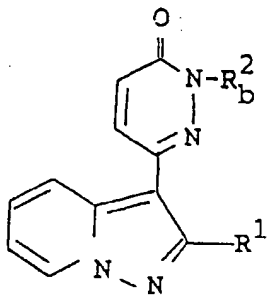
ii) le fait de soumettre un composé de formule:



dans laquelle

R^1 est tel que défini ci-dessus, et
R^2_a est un imidoalkyle en C_1-C_6,

ou un sel de celui-ci, à une réaction d'élimination du groupe protecteur de l'amino, pour donner un composé de formule:

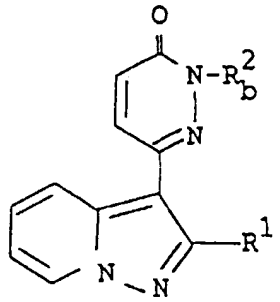


dans laquelle

R^1 est tel que défini ci-dessus, et
R^2_b est un aminoalkyle en C_1-C_6,

ou un sel de celui-ci, ou

iii) le fait de réagir un composé de formule:



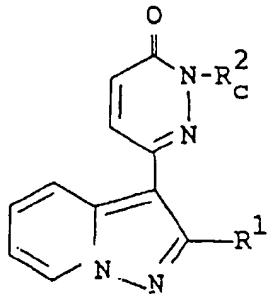
dans laquelle R^1 et R^2_b sont chacun tels que définis ci-dessus,
ou un sel de celui-ci, avec un composé de formule:

$$R^3 - Y$$

dans laquelle

R^3 est un alkyle en C_1-C_6, un carboxyalkyle en C_1-C_6, un alcoxy(en C_1-C_6)carbonylalkyle en C_1-C_6 ou un alkyle en C_1-C_6 ayant un hydroxy et un naphtyloxy, et
Y est un groupe partant,

ou un sel de celui-ci, pour donner un composé de formule:



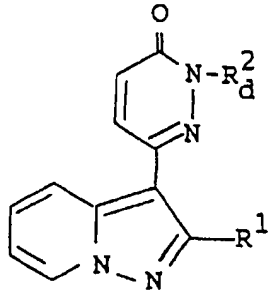
dans laquelle

R^1 est tel que défini ci-dessus, et

R^2_c est un alkyl(en C_1-C_6)aminoalkyle en C_1-C_6, un carboxyalkyl(en C_1-C_6)aminoalkyle en C_1-C_6, un alcoxy (en C_1-C_6)carbonylalkyl(en C_1-C_6)aminoalkyle en C_1-C_6 ou un alkyl(en C_1-C_6)aminoalkyle en C_1-C_6 ayant un hydroxy et un naphtyloxy,

ou un sel de celui-ci, ou

iv) le fait de soumettre un composé de formule:

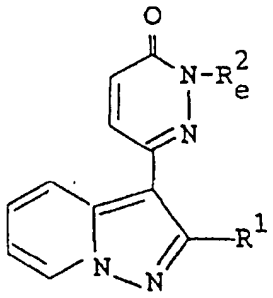


dans laquelle

R^1 est tel que défini ci-dessus, et

R^2_d est un alcoxy(en C_1-C_6)carbonylalkyl(en C_1-C_6)aminoalkyle en C_1-C_6,

ou un sel de celui-ci, à une réaction d'élimination du groupe protecteur du carboxy, pour donner un composé de formule:

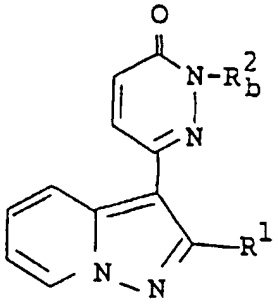


dans laquelle

R^1 est tel que défini ci-dessus, et
R^2_e est un carboxyalkyl(en C_1-C_6)aminoalkyle en C_1-C_6,

ou un sel de celui-ci, ou

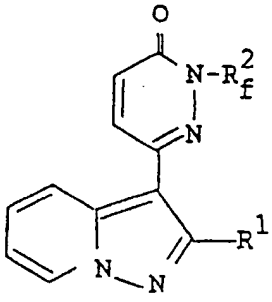
v) le fait de faire réagir un composé de formule:



dans laquelle R^1 et R^2_b sont chacun tels que définis ci-dessus,
ou un sel de celui-ci, avec un composé de formule:

$$H - R^4$$

dans laquelle R^4 est un alkyle en C_1-C_6 ayant un époxy et un naphtyloxy, pour donner un composé de formule:

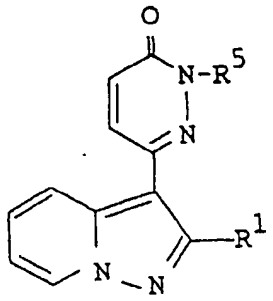


dans laquelle

R^1 est tel que défini ci-dessus, et
R^2_f est un alkyl(en C_1-C_6)aminoalkyle en C_1-C_6 ayant un hydroxy et un naphtyloxy,

ou un sel de celui-ci, ou

vi) le fait de faire réagir un composé de formule:



dans laquelle

R^1 est tel que défini ci-dessus, et
R^5 est un hydroxyalkyle en C_1-C_6,

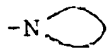
ou son dérivé réactif au groupe hydroxy
ou un sel de celui-ci, avec un composé de formule:

$$H - R^6$$

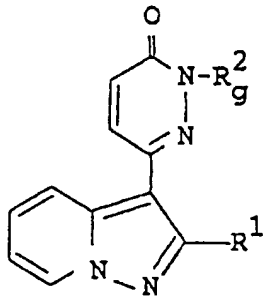
dans laquelle

R^6 est un amino; un alkyl(en C_1-C_6)amino; un carboxyalkyl(en C_1-C_6)amino; un alcoxy(en C_1-C_6)carbonylalkyl(en C_1-C_6)amino; un alkyl(en C_1-C_6)amino ayant un hydroxy et un naphtyloxy; un groupe de formule:

[dans laquelle

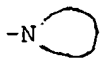


est un groupe hétérocyclique contenant N choisi dans le groupe constitué par un pyridyle, un tétrazolyle, un pipéridyle, un pipérazinyle, un morpholinyle, un oxazolidinyle et un tétrahydropyranyle, dans lequel le groupe hétérocyclique peut avoir 1 à 3 substituants appropriés choisis dans le groupe constitué par un hydroxyalkyle en C_1-C_6, un oxo et un phényle qui peut avoir un alcoxy en C_1-C_6]; ou un imido,
ou un sel de celui-ci, pour donner un composé de formule:



dans laquelle

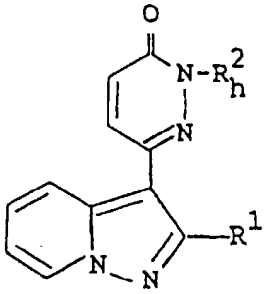
R^1 est tel que défini ci-dessus, et
R^2_g est un aminoalkyle en C_1-C_6;
un alkyl(en C_1-C_6)aminoalkyle en C_1-C_6;
un carboxyalkyl(en C_1-C_6)aminoalkyle en C_1-C_6; un alcoxy(en C_1-C_6)carbonylalkyl(en C_1-C_6)aminoalkyle en C_1-C_6; un alkyl(en C_1-C_6)aminoalkyle en (C_1-C_6) ayant un hydroxy et un naphtyloxy; un alkyle en C_1-C_6 ayant un groupe de formule:



[dans laquelle

est tel que défini ci-dessus]; ou un imidoalkyle en C_1-C_6,
ou un sel de celui-ci, ou

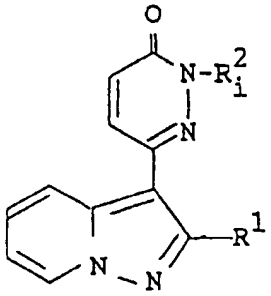
vii) le fait de soumettre un composé de formule:



dans laquelle

R^1 est tel que défini ci-dessus, et
R^2_h est un cyanoalkyle en C_1-C_6 ou un cyanoalkyle en C_7-C_{20},

ou un sel de celui-ci, à une réaction de formation d'un groupe tétrazolyle pour donner un composé de formule:

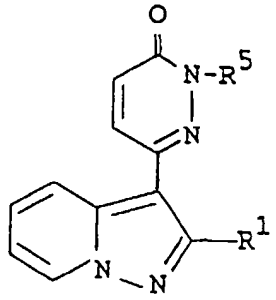


dans laquelle

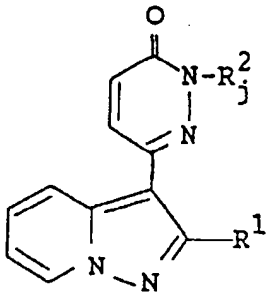
R^1 est tel que défini ci-dessus, et
R^2_i est un tétrazolylalkyle en C_1-C_6 ou un tétrazolylalkyle en C_7-C_{20},

ou un sel de celui-ci, ou

viii) le fait de soumettre un composé de formule:



dans laquelle R^1 et R^5 sont chacun tels que définis ci-dessus,
ou un sel de celui-ci, à une réaction de déshydratation, pour donner un composé de formule:

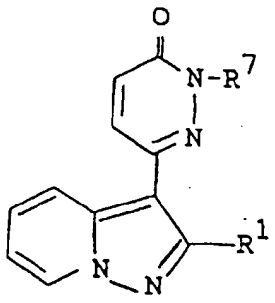


dans laquelle

R^1 est tel que défini ci-dessus, et
R^2_j est un alcényle en C_2-C_4,

ou un sel de celui-ci, ou

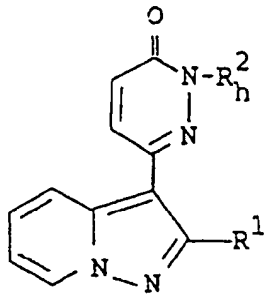
ix) le fait de soumettre un composé de formule:



dans laquelle

R^1 est tel que défini ci-dessus, et
R^7 est un haloalkyle en C_1-C_6,

ou un sel de celui-ci, à une réaction de cyanation, pour donner un composé de formule:



dans laquelle

R^1 est tel que défini ci-dessus, et
R^2_h est un cyanoalkyle en C_1-C_6,

ou un sel de celui-ci.

4. Composition pharmaceutique qui comprend, en tant que ingrédient actif, un composé de la revendication 1 ou un sel pharmaceutiquement acceptable de celui-ci en mélange avec un support ou un excipient pharmaceutiquement acceptable.

5. Composé de la revendication 1 et un sel pharmaceutique de celui-ci pour une utilisation comme médicament.

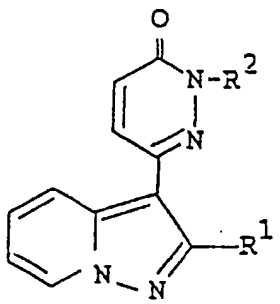
6. Utilisation d'un composé de la revendication 1 ou d'un sel pharmaceutiquement acceptable de celui-ci pour la fabrication d'un médicament.

7. Composé de la revendication 1 et un sel pharmaceutiquement acceptable de celui-ci pour une utilisation dans le traitement et/ou la prévention de la mélancolie, de l'arrêt cardiaque, de l'hypertension, de la défaillance rénale, de la toxicité rénale, de la néphrose, de la néphrite, de l'oedème, de l'obésité, de l'asthme bronchique, de la goutte, de l'hyperuricémie, du syndrome de la mort subite chez l'enfant, de l'immunodépression, des diabètes, de l'ulcères, de la pancréatite, de l'infarctus du myocarde, de la thrombose, de l'obstruction, de l'artériosclérose oblitérante, de la thrombophlébite, de l'infarctus cérébral, de l'attaque ischémique de courte durée ou de l'angine de poitrine.

8. Composition pharmaceutique selon la revendication 4, qui est un antagoniste de l'adénosine.

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé pour la préparation d'un composé de pyrazolopyridine ayant la formule suivante:

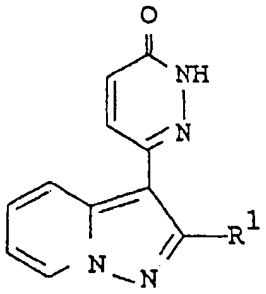


dans laquelle

R^1 est un phényle, et
R^2 est un aminoalkyle en C_1-C_6;
un alkyl(en C_1-C_6)aminoalkyle en C_1-C_6;
un carboxyalkyl(en C_1-C_6)aminoalkyle en C_1-C_6; un alcoxy(en C_1-C_6)carbonylalkyl(en C_1-C_6)aminoalkyle en C_1-C_6; un alkyl(en C_1-C_6)aminoalkyle en C_1-C_6 ayant un hydroxy et un naphtyloxy; un imidoalkyle en C_1-C_6; un cyanoalkyle en C_1-C_6; un alkyle en C_1-C_6 ayant un groupe hétérocyclique choisi dans le groupe constitué par un pyridyle, un tétrazolyle, un pipéridyle, un pipérazinyle, un morpholinyle, un oxazolidinyle et un tétrahydropyranyle, dans lequel le groupe hétérocyclique peut avoir 1 à 3 substituants appropriés choisis dans le groupe constitué par un hydroxyalkyle en C_1-C_6, un oxo et un phényle qui peut avoir un alcoxy en C_1-C_6; un alkyle en C_7-C_{20} ayant un tétrazolyle; un phénylalkyle en C_1-C_6; un alcényle en C_2-C_4; ou un dihydrochrométhyle qui peut avoir 1 à 4 substituants appropriés choisis dans le groupe constitué par un alkyle en C_1-C_6, un hydroxy et un cyano,

et d'un sel pharmaceutiquement acceptable de celui-ci, qui comprend

i) le fait de faire réagir un composé de formule:



dans laquelle R^1 est tel que défini ci-dessus,
ou un sel de celui-ci, avec un composé de formule:

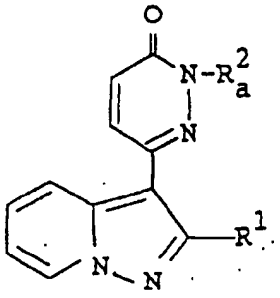
$$R^2 - X$$

dans laquelle

R^2 est tel que défini ci-dessus, et
X est un groupe partant,

ou un sel de celui-ci, ou

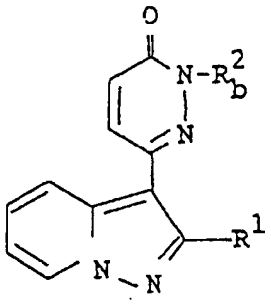
ii) le fait de soumettre un composé de formule:



dans laquelle

R^1 est tel que défini ci-dessus, et
R^2_a est un imidoalkyle en C_1-C_6,

ou un sel de celui-ci, à une réaction d'élimination du groupe protecteur de l'amino, pour donner un composé de formule:

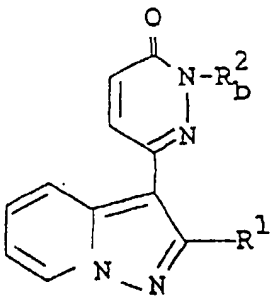


dans laquelle

R^1 est tel que défini ci-dessus, et
R^2_b est un aminoalkyle en C_1-C_6,

ou un sel de celui-ci, ou

iii) le fait de réagir un composé de formule:



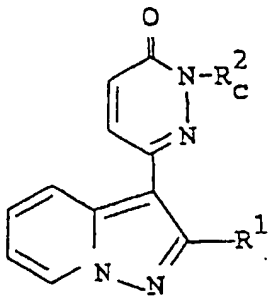
dans laquelle R^1 et R^2_b sont chacun tels que définis ci-dessus,
ou un sel de celui-ci, avec un composé de formule:

$$R^3 - Y$$

dans laquelle

R^3 est un alkyle en C_1-C_6, un carboxyalkyle en C_1-C_6, un alcoxy(en C_1-C_6)carbonylalkyle en C_1-C_6 ou un alkyle en C_1-C_6 ayant un hydroxy et un naphtyloxy, et
Y est un groupe partant,

ou un sel de celui-ci, pour donner un composé de formule:



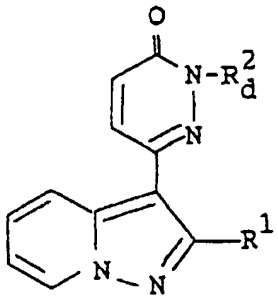
dans laquelle

R^1 est tel que défini ci-dessus, et

R^2_c est un alkyl(en C_1-C_6)aminoalkyle en C_1-C_6, un carboxyalkyl(en C_1-C_6)aminoalkyle en C_1-C_6, un alcoxy (en C_1-C_6)carbonylalkyl(en C_1-C_6)aminoalkyle en C_1-C_6 ou un alkyl(en C_1-C_6)aminoalkyle en C_1-C_6 ayant un hydroxy et un naphtyloxy,

ou un sel de celui-ci, ou

iv) le fait de soumettre un composé de formule:

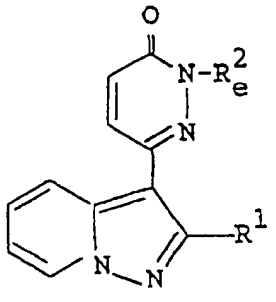


dans laquelle

R^1 est tel que défini ci-dessus, et

R^2_d est un alcoxy(en C_1-C_6)carbonylalkyl(en C_1-C_6)aminoalkyle en C_1-C_6,

ou un sel de celui-ci, à une réaction d'élimination du groupe protecteur du carboxy, pour donner un composé de formule:

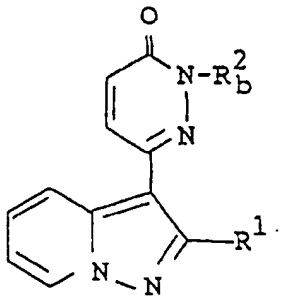


dans laquelle

R^1 est tel que défini ci-dessus, et
R^2_e est un carboxyalkyl(en C_1-C_6)aminoalkyle en C_1-C_6,

ou un sel de celui-ci, ou

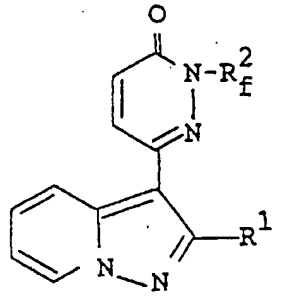
v) le fait de faire réagir un composé de formule:



dans laquelle R^1 et R^2_b sont chacun tels que définis ci-dessus, ou un sel de celui-ci, avec un composé de formule

$$H - R^4$$

dans laquelle R^4 est un alkyle en C_1-C_6 ayant un époxy et un naphtyloxy, pour donner un composé de formule:

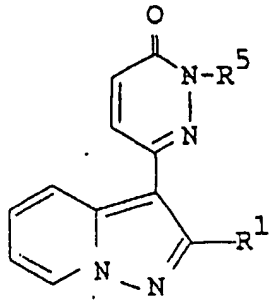


dans laquelle

R^1 est tel que défini ci-dessus, et
R^2_f est un alkyl(en C_1-C_6)aminoalkyle en C_1-C_6 ayant un hydroxy et un naphtyloxy,

ou un sel de celui-ci, ou

vi) le fait de faire réagir un composé de formule:



dans laquelle

R^1 est tel que défini ci-dessus, et
R^5 est un hydroxyalkyle en C_1-C_6,

ou son dérivé réactif au groupe hydroxy
ou un sel de celui-ci, avec un composé de formule:

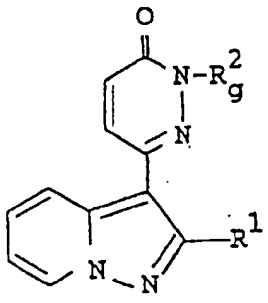
$$H - R^6$$

dans laquelle

R^6 est un amino; un alkyl(en C_1-C_6)amino; un carboxyalkyl(en C_1-C_6)amino; un alcoxy(en C_1-C_6)carbonylalkyl(en C_1-C_6)-amino; un alkyl(en C_1-C_6)amino ayant un hydroxy et un naphtyloxy; un groupe de formule:

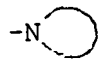
[dans laquelle

est un groupe hétérocyclique contenant N choisi dans le groupe constitué par un pyridyle, un tétrazolyle, un pipéridyle, un pipérazinyle, un morpholinyle, un oxazolidinyle et un tétrahydropyranyle, dans lequel le groupe hétérocyclique peut avoir 1 à 3 substituants appropriés choisis dans le groupe constitué par un hydroxyalkyle en C_1-C_6, un oxo et un phényle qui peut avoir un alcoxy en C_1-C_6]; ou un imido,
ou un sel de celui-ci, pour donner un composé de formule:



dans laquelle

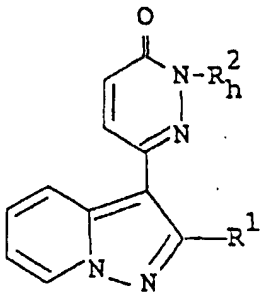
R^1 est tel que défini ci-dessus, et
R^2_g est un aminoalkyle en C_1-C_6; un alkyl(en C_1-C_6)aminoalkyle en C_1-C_6; un carboxyalkyl(en C_1-C_6)aminoalkyle en C_1-C_6; un alcoxy(en C_1-C_6)carbonylalkyl(en C_1-C_6)aminoalkyle en C_1-C_6; un alkyl(en C_1-C_6)aminoalkyle en (C_1-C_6) ayant un hydroxy et un naphtyloxy; un alkyle en C_1-C_6 ayant un groupe de formule:



[dans laquelle

est tel que défini ci-dessus]; ou un imidoalkyle en C_1-C_6,
ou un sel de celui-ci, ou

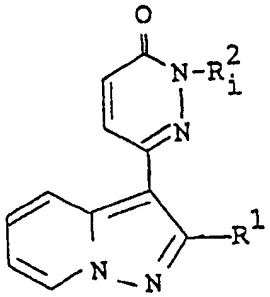
vii) le fait de soumettre un composé de formule:



dans laquelle

R^1 est tel que défini ci-dessus, et
R^2_h est un cyanoalkyle en C_1-C_6 ou un cyanoalkyle en C_7-C_{20},

ou un sel de celui-ci, à une réaction de formation d'un groupe tétrazolyle pour donner un composé de formule:

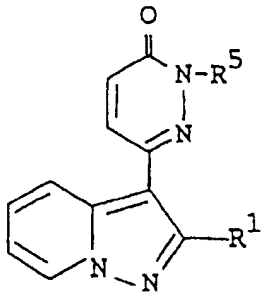


dans laquelle

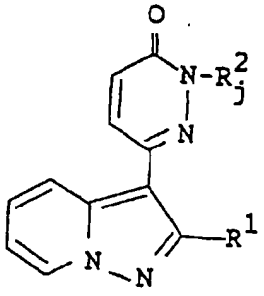
R^1 est tel que défini ci-dessus, et
R^2_i est un tétrazolylalkyle en C_1-C_6 ou un tétrazolylalkyle en C_7-C_{20},

ou un sel de celui-ci, ou

viii) le fait de soumettre un composé de formule:



dans laquelle R^1 et R^5 sont chacun tels que définis ci-dessus,
ou un sel de celui-ci, à une réaction de déshydratation, pour donner un composé de formule:

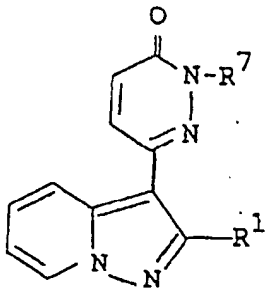


dans laquelle

R^1 est tel que défini ci-dessus, et
R^2_j est un alcényle en C_2-C_4,

ou un sel de celui-ci, ou

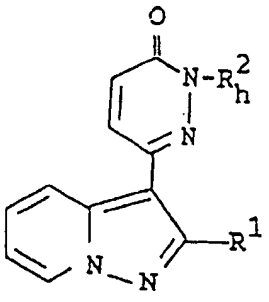
ix) le fait de soumettre un composé de formule:



dans laquelle

R^1 est tel que défini ci-dessus, et
R^7 est un haloalkyle en C_1-C_6,

ou un sel de celui-ci, à une réaction de cyanation, pour donner un composé de formule:



dans laquelle

R^1 est tel que défini ci-dessus, et
R^2_h est un cyanoalkyle en C_1-C_6,

ou un sel de celui-ci.

2. Procédé selon la revendication 1, dans lequel R^2 est un alkyl(en C_1-C_6)aminoalkyle en C_1-C_6; un alkyle en C_1-C_6 ayant un tétrazolyle, un pipéridyle ou un morpholinyle; ou un alkyle en C_7-C_{20} ayant un tétrazolyle.

3. Modification des procédés selon les revendications 1 ou 2 qui comprend le fait de combiner le composé de pyrazolopyridine obtenu avec un support pharmaceutiquement acceptable non-toxique habituel.